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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 4.2018— February 12, 2018

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Multiple Myeloma

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here:](#)
nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus:
All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#)

NCCN Categories of Preference:
All recommendations are considered appropriate.

See [NCCN Categories of Preference](#)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2018.



NCCN Guidelines Version 4.2018

Multiple Myeloma

Updates in Version 4.2018 of the NCCN Guidelines for Multiple Myeloma from Version 3.2018 include:

[MYEL-4](#)

- Active (symptomatic) myeloma, primary treatment: added denosumab as an option for the prevention of skeletal-related events for all patients receiving primary treatment.

[MYEL-E](#)

- Supportive care treatment for multiple myeloma, bone disease, removed first bullet "~~Bisphosphonates (pamidronate, and zoledronic acid)~~¹."
- Modified "All patients receiving primary myeloma therapy should be given bisphosphonates¹ (category 1)" by adding "*or denosumab*."²
- Modified the bullet "A *baseline* dental exam is recommended ~~before starting bisphosphonate therapy~~."
- Modified "Monitor for renal dysfunction with use of bisphosphonate *therapy*."
- Footnote 2 is new to the page "Denosumab is preferred in patients with renal insufficiency."

Updates in Version 3.2018 of the NCCN Guidelines for Multiple Myeloma from Version 2.2018 include:

[Discussion](#)

- The Discussion section was updated to reflect the changes in the algorithm.

Updates in Version 2.2018 of the NCCN Guidelines for Multiple Myeloma from Version 1.2018 include:

[MYEL-D \(1 of 3\)](#)

- Primary therapy for transplant candidates:
- Changed the NCCN Category of Evidence and Consensus from a category 2B to a category 2A for carfilzomib/lenalidomide/dexamethasone.

[MYEL-D \(2 of 3\)](#)

- Primary therapy for non-transplant candidates:
 - Changed the NCCN Category of Evidence and Consensus from a category 2B to a category 2A for the following regimens:
 - ◇ Carfilzomib/lenalidomide/dexamethasone
 - ◇ Ixazomib/lenalidomide/dexamethasone
 - ◇ Carfilzomib/cyclophosphamide/dexamethasone

[Continued on next page](#)

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Multiple Myeloma

Updates in Version 1.2018 of the NCCN Guidelines for Multiple Myeloma from Version 3.2017 include:

General:

- The [NCCN Categories of Preference](#) have been added to this version of the guidelines.

MYEL-1

- Initial diagnostic workup:
 - ▶ Added "Exam of peripheral blood smear"
 - ▶ Added "Creatinine clearance (calculated or measured directly)"
 - ▶ Added "Serum uric acid"
 - ▶ Modified "Skeletal survey *or whole body low-dose CT scan*"
 - ▶ Added "t(14:20)" and "1p abnormality"
- Useful in certain circumstances:
 - ▶ Removed "Whole body low-dose CT scan"
 - ▶ Modified "Whole body *or skeletal* MRI or whole body PET/CT scan"
 - ▶ Removed "Bone densitometry"
 - ▶ Added "Echocardiogram"
 - ▶ Replaced "Staining of marrow and fat pad for amyloid" with "Evaluate for light chain amyloidosis, if appropriate."
- Clinical presentation, removed footnote from smoldering (asymptomatic) and added it to active (symptomatic).
- Modified footnote "a", "whole body *or skeletal* MRI..."
- Removed footnote "d", "Includes Durie-Salmon Stage I Myeloma."

MYEL-2

- Primary treatment, added "in 1.8–2.0 Gy/fraction" to radiation recommendations.
- Serum FLC assay, added "as clinically indicated."
- Follow-up/surveillance, added a new footnote to "Follow-up interval, every 3–6 mo." The new footnote states "Patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up."

MYEL-3

- Follow-up/surveillance:
 - ▶ Removed "Serum BUN"
 - ▶ Modified "Skeletal survey *or whole body low-dose CT scan as indicated*" and removed "annually or for symptoms."

- ▶ Modified "Whole body *or skeletal* MRI as clinically indicated"
- Updated reference in footnote "g" Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smoldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17(8):1117-1136.
- ▶ Modified sentence, "Alternative criteria *have been described*."

MYEL-4

- Follow-up/surveillance:
 - ▶ Removed "Serum BUN"
 - ▶ Modified "Skeletal survey *or whole body low-dose CT scan as indicated*" and removed "annually or for symptoms."
 - ▶ Modified "Whole body *or skeletal* MRI as clinically indicated"
 - ▶ Modified "Bone marrow aspirate and biopsy *at relapse with FISH* as clinically indicated."
 - ▶ Removed "and If candidate for transplantation" replaced with "Assess for stem cell transplant candidacy"
 - ▶ Changed "Harvest stem cell (adequate for 2 transplants)" to "Harvest stem cells (*consider* for 2 transplants)."
- Modified footnote: "Autologous transplantation: Category 1 evidence supports proceeding *directly straight* after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant."

MYEL-5

- Follow-up/surveillance:
 - ▶ Removed "Serum BUN"
 - ▶ Modified "Skeletal survey *or whole body low-dose CT scan as indicated*" removed "annually or for symptoms."
 - ▶ Removed "Whole body MRI as clinically indicated."
- Modified footnote "A majority of phase 3 trials do not show a survival advantage for allogeneic SCT compared with autologous SCT." Also abbreviated references listed by removing the titles.

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Updates in Version 1.2018 of the NCCN Guidelines for Multiple Myeloma from Version 3.2017 include:

MYEL-6

- **Active (symptomatic) myeloma:**
 - ▶ Removed footnote "Response to treatment as determined by the follow-up tests listed on MYEL-4."
 - ▶ Removed footnote "There is evidence from a randomized, phase III trial showing that maintenance therapy after tandem transplant significantly reduced the risk of disease progression (HR, 0.47). Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371:895-905."
 - ▶ Combined footnotes "Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2–3 y minimum length of remission for consideration of a second autologous stem cell transplant."
 - ▶ Post-autologous stem cell transplant, added "(single or tandem)."
 - ▶ Added "category 1" to maintenance therapy
 - ▶ Added "clinical trial"
 - ▶ Removed "Tandem transplant ± maintenance therapy or Observe"

MYEL-7

- **Active (symptomatic) myeloma, combined pathways into one pathway for "Relapse or progressive disease."**
- **Added "or Autologous stem cell transplant."**
- **Added a footnote "Assess for stem cell transplant candidacy."**
- **Added "Refractory disease and lack of treatment options."**

MYEL-A

- ▶ **Smoldering (asymptomatic) myeloma, removed "IgG or IgA"**
- Modified footnote "Other examples of active disease include: repeated infections, amyloidosis, *light chain deposition disease*, or hyperviscosity."**

MYEL-C

- **Minimal response, changed "≥50%" to "25%–49%."**

MYEL-D (1 of 3)

- **Primary therapy for transplant candidates:**
 - ▶ Changed "Assess for response after 2 cycles" to "Assess for response after each cycle."
 - ▶ Added a new category, "Useful in Certain Circumstances."
 - ▶ **Preferred Regimens:**
 - ◊ Moved "bortezomib/doxorubicin/dexamethasone" to "Other Recommended Regimens."
 - ◊ Added a footnote to bortezomib/cyclophosphamide/dexamethasone, "Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves."
 - ▶ **Other Recommended Regimens:**
 - ◊ Moved "bortezomib/dexamethasone (category 1)" to "Useful in Certain Circumstances."
 - ◊ Moved "bortezomib/thalidomide/dexamethasone (category 1)" to "Useful in Certain Circumstances."
 - ◊ Moved "lenalidomide/dexamethasone (category 1)" to "Useful in Certain Circumstances."
 - ◊ Added "Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)"
 - ▶ **Modified footnote 2: "Recommend Herpes zoster prophylaxis for patients treated with proteasome inhibitors *or daratumumab*."**
 - ▶ **Modified footnote 3: "Subcutaneous bortezomib is the preferred method of administration." ~~for patients with pre-existing or high-risk peripheral neuropathy~~**

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Multiple Myeloma

Updates in Version 1.2018 of the NCCN Guidelines for Multiple Myeloma from Version 3.2017 include:

MYEL-D (2 of 3)

- Primary therapy for non-transplant candidates:
 - Changed "Assess for response after 2 cycles" to "Assess for response after each cycle."
 - Updated reference in footnote, "Continuously until progression. *Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.*"
 - Added a new category, "Useful in Certain Circumstances."
 - Other Recommended Regimens:
 - ◊ Added "Carfilzomib/cyclophosphamide/dexamethasone (category 2B)."
 - ◊ Moved "bortezomib/dexamethasone (category 1) to "Useful in Certain Circumstances."
- Maintenance therapy
 - Separated to "Preferred Regimens" and "Other Recommended Regimens"
 - Preferred Regimens:
 - ◊ Moved "bortezomib" to "Other Recommended Regimens."

MYEL-D (3 of 3)

- Therapy for Previously Treated Multiple Myeloma:
 - Added a new category, "Useful in Certain Circumstances."
 - Preferred Regimens:
 - ◊ Moved "bortezomib/cyclophosphamide/dexamethasone" to "Other Recommended Regimens."
 - ◊ Moved "lenalidomide/dexamethasone" to "Other Recommended Regimens."
 - ◊ Moved "pomalidomide/dexamethasone" to "Other Recommended Regimens."
 - ◊ Moved "pomalidomide/carfilzomib/dexamethasone" to "Other Recommended Regimens."
 - Other Recommended Regimens:
 - ◊ Added "carfilzomib/dexamethasone (weekly)"
 - ◊ Added "dexamethasone" to "bortezomib/liposomal doxorubicin"

- ◊ Added "daratumumab/pomalidomide/dexamethasone."
- ◊ Added "ixazomib/pomalidomide/dexamethasone."
- ◊ Added "panobinostat/lenalidomide/dexamethasone."
- ◊ Moved "bendamustine" to "Useful in Certain Circumstances."
- ◊ Moved "dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)" to "Useful in Certain Circumstances."
- ◊ Moved "Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide(DT-PACE) ± bortezomib (VTD-PACE)" to "Useful in Certain Circumstances."
- ◊ Moved "High-dose cyclophosphamide" to "Useful in Certain Circumstances."

MYEL-E

- Bone disease, changed "annually and if symptomatic" to "if clinically indicated."
- Low-dose RT, added "(8 Gy x 1 fx, or 10–30 Gy in 2.0–3.0 Gy fractions)."
- Hypercalcemia, removed "furosemide" and added "denosumab."
- Anemia, added "Type and screen should be performed before using daratumumab."
- Infection, modified bullet: "The pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later."
 - Modified " Herpes zoster prophylaxis for all patients treated with proteasome inhibitors *or* daratumumab."
- Renal dysfunction, added "Consider renal biopsy if clinically indicated."
 - Removed "Not a contraindication to transplant."

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Multiple Myeloma

INITIAL DIAGNOSTIC WORKUP

- History and physical exam
- CBC, differential, platelet count
- Exam of peripheral blood smear
- Serum BUN/creatinine, electrolytes, albumin, and calcium
- Creatinine clearance (calculated or measured directly)
- Serum uric acid
- Serum LDH and beta-2 microglobulin
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Skeletal survey or whole body low-dose CT scan
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Metaphase cytogenetics on bone marrow
- Plasma cell FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14;20), 1q21 amplification], 1p abnormality

Useful in Certain Circumstances

- Whole body or skeletal MRI or whole body PET/CT scan^a
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Plasma cell proliferation
- Serum viscosity
- HLA typing
- Echocardiogram
- Evaluate for light chain amyloidosis, if appropriate

[See NCCN Guidelines for Systemic Light Chain Amyloidosis](#)

CLINICAL PRESENTATION

Solitary plasmacytoma^b

Smoldering (asymptomatic)^{b,c}

Active (symptomatic)^b

[See Solitary Osseous: Primary Treatment \(MYEL-2\)](#)

[See Solitary Extraosseous: Primary Treatment \(MYEL-2\)](#)

[See Primary Treatment \(MYEL-3\)](#)

[See Primary Treatment \(MYEL-4\)](#)

^aAdditional testing (whole body or skeletal MRI or whole body PET/CT scan) is recommended to discern active from smoldering myeloma, if skeletal survey is negative. Recommendations for MRI are with contrast.

^b[See Staging Systems for Multiple Myeloma \(MYEL-B\).](#)

^c[See Definition of Multiple Myeloma \(Smoldering and Active\) \(MYEL-A\).](#)

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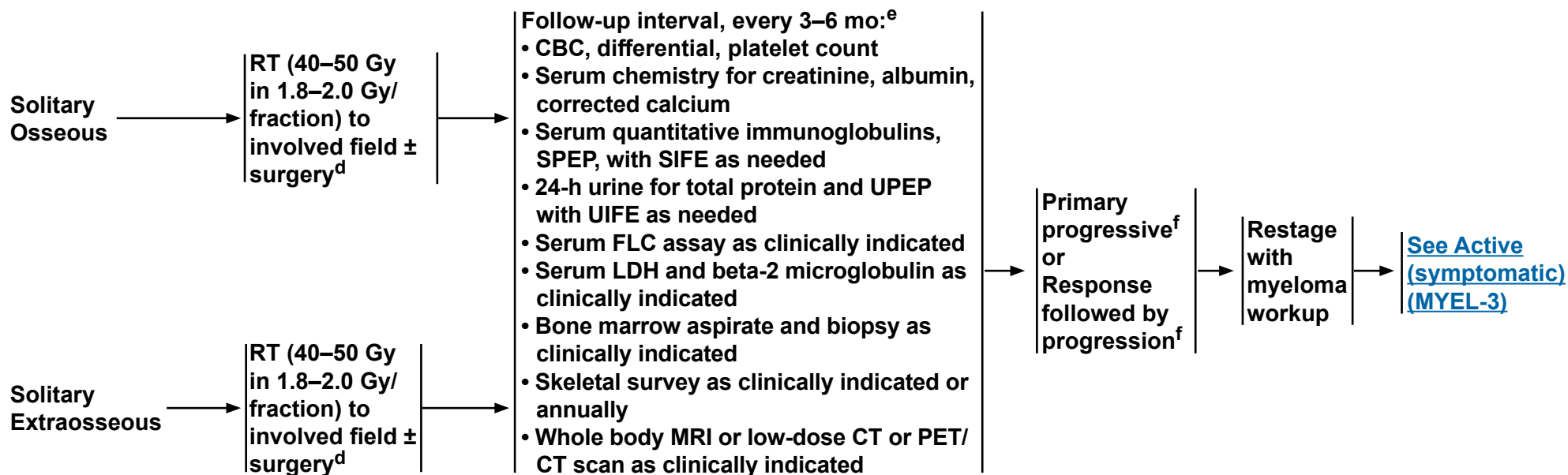
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Multiple Myeloma

CLINICAL PRESENTATION

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE


^dConsider surgery if structurally unstable or if there are neurological compression issues.

^ePatients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up.

^f[See Response Criteria for Multiple Myeloma \(MYEL-C\)](#).

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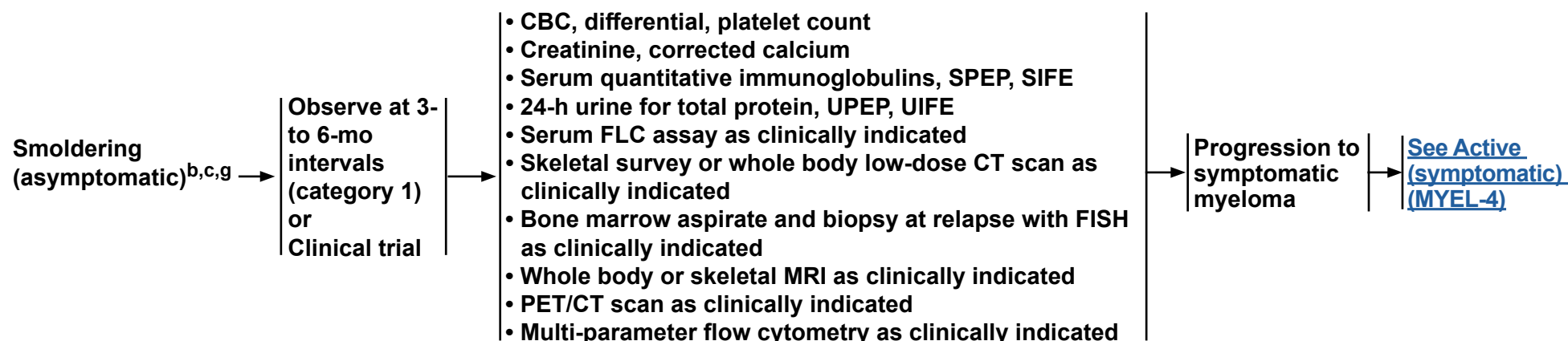
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CLINICAL PRESENTATION

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE



^bSee [Staging Systems for Multiple Myeloma \(MYEL-B\)](#).

^cSee [Definition of Multiple Myeloma \(Smoldering and Active\) \(MYEL-A\)](#).

^gA relatively small randomized prospective study has shown benefit of early treatment with lenalidomide and dexamethasone for a subset of patients with smoldering myeloma with certain high-risk features predictive for early clinical progression Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smoldering multiple myeloma (QuiRedex): long-term follow-up of a randomized, controlled, phase 3 trial. *Lancet Oncol* 2016;17(8):1127-1136. However, the high-risk criteria specified in the study are not in common use. Alternative criteria have been described (Dispienzeri A, Kyle R, Katzmman J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111(2):785-789). The NCCN panel strongly recommends enrolling eligible smoldering myeloma patients with high-risk criteria in clinical trials.

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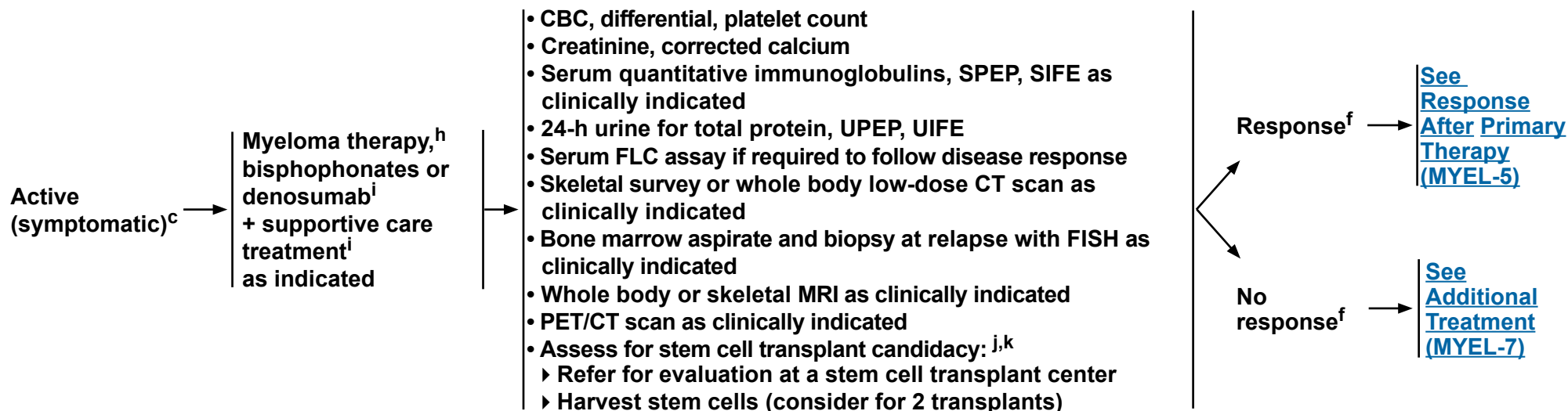
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CLINICAL PRESENTATION

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE



^cSee Definition of Multiple Myeloma (Smoldering and Active) (MYEL-A).

^fSee Response Criteria for Multiple Myeloma (MYEL-C).

^hSee Myeloma Therapy (MYEL-D).

ⁱSee Supportive Care Treatment for MM (MYEL-E).

^jAutologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. [\(See Discussion section\).](#)

^kRenal dysfunction and advanced age are not contraindications to transplant.

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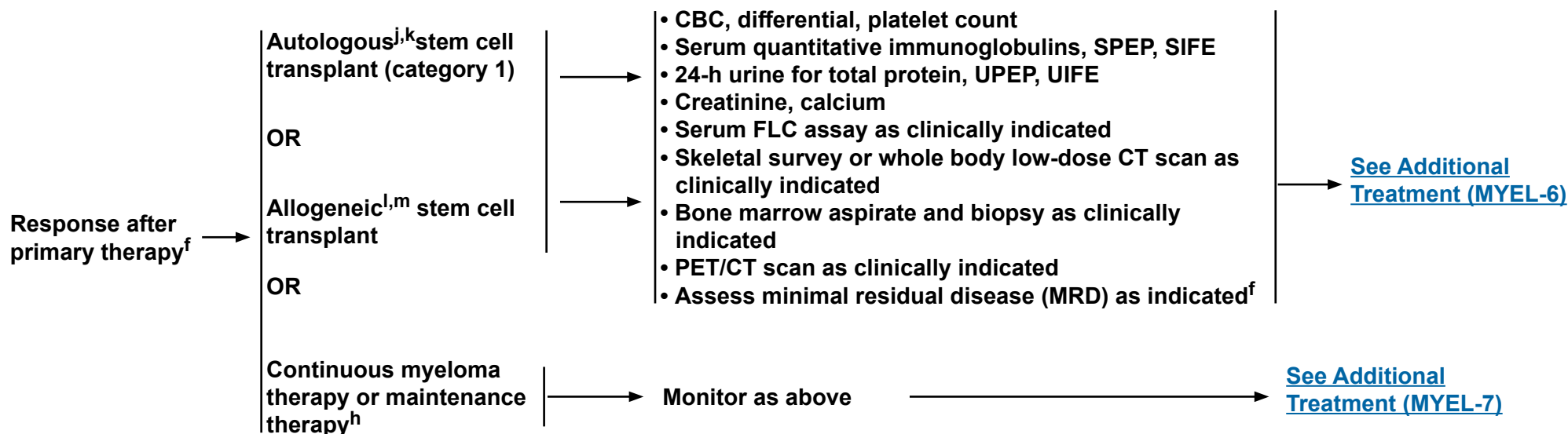


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ACTIVE (SYMPTOMATIC) MYELOMA

FOLLOW-UP/SURVEILLANCE



^fSee Response Criteria for Multiple Myeloma (MYEL-C).

^hSee Myeloma Therapy (MYEL-D).

^jAutologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. (See Discussion section).

^kRenal dysfunction and advanced age are not contraindications to transplant.

^lAllogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably in a clinical trial. Current data do not support miniallografting alone.

^mA majority of phase 3 trials do not show a survival advantage for allogeneic SCT compared with autologous SCT. (See Discussion section).

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Multiple Myeloma

ACTIVE (SYMPTOMATIC) MYELOMA

ADDITIONAL TREATMENT

Post-allogeneic stem cell transplant:

Progressive disease^f

Response or
stable disease^f

Maintenance therapy
on clinical trial
or
Observe

Progressive disease^f

Therapy for previously treated myeloma^h
or
Clinical trial
or
Donor lymphocyte infusion

Post-autologous stem cell transplant (single or tandem):

Progressive disease^f

Therapy for previously treated myeloma^h
or
Clinical trial
or
Allogeneic stem cell transplant^l

Response or
stable disease^f

Maintenance therapy
(category 1)^h
or
Clinical trial

Progressive disease^f

Therapy for previously treated myeloma^h
or
Clinical trial ± additional autologous stem cell
transplantⁿ
or
Allogeneic stem cell transplant^l

^fSee [Response Criteria of Multiple Myeloma \(MYEL-C\)](#).

^hSee [Myeloma Therapy \(MYEL-D\)](#).

^lAllogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.

ⁿAdditional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2- to 3-y minimum length of remission for consideration of a second autologous stem cell transplant.

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Multiple Myeloma

ACTIVE (SYMPTOMATIC) MYELOMA

ADDITIONAL TREATMENT (FOR PATIENTS TREATED WITH OR WITHOUT A PRIOR TRANSPLANT)



^fSee [Response Criteria for Multiple Myeloma \(MYEL-C\)](#).

^hSee [Myeloma Therapy \(MYEL-D\)](#).

^jAutologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival although progression-free survival can be prolonged by an early transplant. ([See Discussion section](#)).

^lAllogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.

^oAssess for stem cell transplant candidacy.

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Multiple Myeloma

DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

Smoldering (Asymptomatic) Myeloma^{1,2}

- Serum monoclonal protein ≥ 3 g/dL
- Or*
- Bence-Jones protein ≥ 500 mg/24 h
- And/Or*
- Clonal bone marrow plasma cells 10%–60%
- And*
- Absence of myeloma-defining events or amyloidosis
 - ▶ If skeletal survey negative, assess for bone disease with whole body MRI or PET/CT

Active (Symptomatic) Myeloma^{2,3}

Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma

And

Any one or more of the following myeloma-defining events:

- Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency (creatinine >2 mg/dL [>177 $\mu\text{mol/L}$] or creatinine clearance <40 mL/min)
- Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)
- One or more osteolytic bone lesions on skeletal radiography, CT, or PET/CT
- Clonal bone marrow plasma cells $\geq 60\%$
- Abnormal serum FLC ratio ≥ 100 (involved kappa) or ≤ 0.01 (involved lambda)
- >1 focal lesions on MRI studies ≥ 5 mm

¹The understanding of smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics, including IgG levels of >3 g/dL, IgA of >2 g/dL, or urinary Bence Jones protein of >1 g/24 h (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med* 2013;369:438-447) or abnormal free light chain ratios (Dispenzieri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008;111:785-789) have an increased risk of progression to active (symptomatic) myeloma. It is also

increasingly recognized that the classical definition of smoldering myeloma using certain tests such as plain x-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as “asymptomatic” to having “active disease” are underway.

²Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;Vol 15,e538-e548.

³Other examples of active disease include: repeated infections, amyloidosis, light chain deposition disease, or hyperviscosity.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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Multiple Myeloma

STAGING SYSTEMS FOR MULTIPLE MYELOMA¹

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH ² and Serum LDH ≤ the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH ² or Serum LDH > the upper limit of normal

¹Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-2869.

²Standard-risk: No high-risk chromosomal abnormality. High-risk: Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

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Multiple Myeloma

RESPONSE CRITERIA FOR MULTIPLE MYELOMA

(Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)

Response Category	Response Criteria
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years). [†]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF [‡] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10 ⁵ nucleated cells [§] or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue. [¶]
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). ^{††}
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions) ^{§§} of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD ^{§§} of soft tissue plasmacytomas is also required.

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Multiple Myeloma

RESPONSE CRITERIA FOR MULTIPLE MYELOMA (Revised based on the new criteria by International Myeloma Working Group [IMWG])	
Response Category	Response Criteria
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease ^{¶¶,}	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥ 0.5 g/dL); Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; Urine M-protein (absolute increase must be ≥ 200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be $\geq 10\%$); Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD^{§§} of >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion >1 cm in short axis; $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD^{§§} of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein.

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Multiple Myeloma

RESPONSE CRITERIA FOR MULTIPLE MYELOMA

(Revised based on the new criteria by International Myeloma Working Group [IMWG])

Response Category	Response Criteria
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above).
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

*All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

†Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilised mixture of antibodies, which reduces errors, time, and costs. Five million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10⁵ plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood 2012; 119: 687–91.

§DNA sequencing assay on bone marrow aspirate should use a validated assay.

¶Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma Criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax = 2.5 within osteolytic CT areas >1 cm in size, or SUVmax = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. Clin Cancer Res 2015; 21: 4384–90.

||Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response

criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. Durie BG, Harousseau JL, Miguel JS, et al, for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–73.

**All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated serum FLC assay.

††Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

¶¶Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

||||In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328–46, Copyright (2016), with permission from Elsevier."

Note: All recommendations are category 2A unless otherwise indicated.

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Multiple Myeloma

MYELOMA THERAPY¹⁻⁴

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens

- Bortezomib/lenalidomide⁵/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone⁶

Other Recommended Regimens

- Bortezomib/doxorubicin/dexamethasone (category 1)
- Carfilzomib^{7,8}/lenalidomide⁵/dexamethasone
- Ixazomib/lenalidomide⁵/dexamethasone (category 2B)

Useful In Certain Circumstances

- Bortezomib/dexamethasone (category 1)⁹
- Bortezomib/thalidomide/dexamethasone (category 1)
- Lenalidomide⁵/dexamethasone (category 1)⁹
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)

¹Selected, but not inclusive of all regimens.

²Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.

³Subcutaneous bortezomib is the preferred method of administration.

⁴Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

⁵Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

⁶Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

⁷Optimal dosing in this regimen has not been defined.

⁸Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

⁹Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

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Multiple Myeloma

MYELOMA THERAPY¹⁻⁴

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES (assess for response after each cycle)

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)^{9,10}
- Bortezomib/cyclophosphamide/dexamethasone⁶

Other Recommended Regimens

- Carfilzomib⁸/lenalidomide/dexamethasone
- Carfilzomib⁸/cyclophosphamide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

Useful In Certain Circumstances

- Bortezomib/dexamethasone⁹

MAINTENANCE THERAPY

Preferred Regimens

- Lenalidomide¹¹ (category 1)

Other Recommended Regimens

- Bortezomib

¹Selected, but not inclusive of all regimens.

²Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.

³Subcutaneous bortezomib is the preferred method of administration.

⁴Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

⁶Preferred initial treatment in patients with acute renal insufficiency. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

⁸Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

⁹Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

¹⁰Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.

¹¹There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

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Multiple Myeloma

MYELOMA THERAPY^{1-4,12}

Therapy for Previously Treated Multiple Myeloma (assess for response after each cycle)

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)⁸/dexamethasone (category 1)⁹
- Carfilzomib⁸/lenalidomide/dexamethasone (category 1)¹³
- Daratumumab¹⁴/bortezomib/dexamethasone (category 1)
- Daratumumab¹⁴/lenalidomide/dexamethasone (category 1)
- Elotuzumab¹⁵/lenalidomide/dexamethasone (category 1)¹³
- Ixazomib¹⁷/lenalidomide/dexamethasone (category 1)¹³

Other Recommended Regimens

- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib⁸/cyclophosphamide/dexamethasone
- Carfilzomib (weekly)⁸/dexamethasone⁹
- Cyclophosphamide/lenalidomide/dexamethasone
- Bortezomib/dexamethasone (category 1)⁹
- Daratumumab^{14,16}
- Daratumumab¹⁴/pomalidomide²⁰/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib¹⁷/dexamethasone⁹
- Ixazomib/pomalidomide²⁰/dexamethasone
- Lenalidomide/dexamethasone¹⁸ (category 1)⁹
- Panobinostat¹⁹/bortezomib/dexamethasone (category 1)
- Panobinostat¹⁹/carfilzomib^{8,9}
- Panobinostat¹⁹/lenalidomide/dexamethasone
- Pomalidomide²⁰/cyclophosphamide/dexamethasone
- Pomalidomide²⁰/dexamethasone¹⁸ (category 1)⁹
- Pomalidomide²⁰/bortezomib/dexamethasone
- Pomalidomide²⁰/carfilzomib⁸/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)²¹
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)²¹ ± bortezomib (VTD-PACE)²¹
- High-dose cyclophosphamide

¹Selected, but not inclusive of all regimens.

²Herpes zoster prophylaxis for patients treated with proteasome inhibitors or daratumumab.

³Subcutaneous bortezomib is the preferred method of administration.

⁴Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

⁸Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

⁹Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

¹²Consideration for appropriate regimen is based on the context of clinical relapse.

¹³Clinical trials with these regimens primarily included patients who were lenalidomide-naïve or with lenalidomide-sensitive multiple myeloma.

¹⁴May interfere with serological testing and cause false-positive indirect Coombs test. (See MYEL-E)

¹⁵Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.

¹⁶Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.

¹⁷Indicated for the treatment of patients who have received at least one prior therapy.

¹⁸Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.

¹⁹Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

²⁰Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

²¹Generally reserved for the treatment of aggressive multiple myeloma.

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Multiple Myeloma

SUPPORTIVE CARE TREATMENT FOR MM

Bone Disease

- All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)¹ or denosumab²
 - ▶ A baseline dental exam is recommended
 - ▶ Monitor for renal dysfunction with use of bisphosphonate therapy
 - ▶ Monitor for osteonecrosis of the jaw
- Use of bisphosphonates in smoldering or stage I disease preferably in the context of a clinical trial. These patients should have skeletal survey if clinically indicated.
- RT
 - ▶ Low-dose RT (8 Gy x 1 fx, or 10–30 Gy in 2.0–3.0 Gy fractions) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression
 - ▶ Limited involved fields should be used to limit the impact of irradiation on stem-cell harvest or impact on potential future treatments
- Orthopedic consultation should be sought for impending or actual long-bone fractures or bony compression of spinal cord or vertebral column instability
- Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures

Hypercalcemia

- Hydration, bisphosphonates (zoledronic acid preferred), denosumab, steroids, and/or calcitonin

Hyperviscosity

- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

Anemia

- [See NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia](#)

- Consider erythropoietin for anemic patients
- Type and screen should be performed before using daratumumab

Infection

- [See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection
- The pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later.
- *Pneumocystis jiroveci pneumonia* (PJP), herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Herpes zoster prophylaxis for all patients treated with proteasome inhibitors or daratumumab.

Renal Dysfunction

- Maintain hydration to avoid renal failure
- Avoid use of NSAIDs
- Avoid IV contrast
- Plasmapheresis (category 2B)
- Consider renal biopsy if clinically indicated
- Monitor for renal dysfunction with chronic use of bisphosphonates

Coagulation/Thrombosis

- Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
- [See NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#)

¹Both pamidronate and zoledronic acid have shown equivalence in terms of reducing risk of skeletal-related events in randomized trials. In a recent MRC IX trial, in addition to benefits for bone health, zoledronic acid reduced mortality by 16% versus clodronic acid and extended median overall survival by 5.5 months. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomized controlled trial. *Lancet* 2010;376:1989-1999.

²Denosumab is preferred in patients with renal insufficiency.

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Multiple Myeloma

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/22/17

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation)

All recommendations are considered appropriate

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Multiple Myeloma

Overview

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. MM accounts for about 1.8% of all cancers and slightly over 17% of hematologic malignancies in the United States.¹ Myeloma is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.² The American Cancer Society has estimated 30,280 new myeloma cases in the United States in 2017, with an estimated 12,590 deaths.¹

Newly diagnosed MM is typically sensitive to a variety of cytotoxic drugs. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches. Treatment of MM has been rapidly evolving with the introduction of new classes and newer generation of drugs: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, and histone deacetylase (HDAC) inhibitors. In addition, there is increasing understanding of the tumor biology, creating the rationale for new combinations of therapies and new drug development.^{3,4} Studies of the associated cytogenetic abnormalities indicate that MM is a heterogeneous disease, suggesting that risk-adapted approaches and individualizing treatment will further help refine patient management.

These guidelines developed by the NCCN Multiple Myeloma Panel Members address diagnosis, treatment, and follow-up for patients with MM.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Multiple Myeloma, an electronic search of the PubMed database was performed

to obtain key literature in MM published between April 1, 2016 and May 3, 2017, using the following search terms: Smoldering Myeloma OR Multiple Myeloma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.⁵

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The results of the PubMed search were examined for their potential relevance. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

Diagnosis and Workup

The initial diagnostic workup in all patients should include a history and physical examination and the following baseline blood studies and biological assessments to differentiate symptomatic and asymptomatic MM: a complete blood count (CBC) with differential and platelet counts; examination of peripheral blood smear; blood urea nitrogen (BUN); serum creatinine; creatinine clearance (calculated or measured directly)



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and serum electrolytes; serum calcium; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin.

Peripheral smear may show abnormal distribution of red blood cells such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.⁶ Increased BUN and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell burden.

Serum and Urine Analysis: The monoclonal protein (M-protein) components in serum and urine are evaluated by the following urine and serum analyses.

Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM); serum protein electrophoresis (SPEP); and serum immunofixation electrophoresis (SIFE) to obtain more specific information about the type of M-protein present. Assessing changes in levels of various proteins, particularly the M-protein, helps track disease progression and response to treatment. Urine analysis as a part of the initial diagnostic workup includes evaluating 24-hour urine for total protein; urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE).

Free Light-chain Assay: Use of serum free light-chain (FLC) assay along with SPEP and SIFE yields high sensitivity while screening for MM and related plasma cell disorders.⁷ Therefore, this assay is now included as a part of the initial diagnostic workup in the NCCN Guidelines for Multiple Myeloma. The serum FLC assay also has prognostic value in plasma cell disorders, including monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active myeloma, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.^{7,8} The serum FLC assay also allows for

quantitative monitoring of patients with light chain amyloidosis and oligosecretory myeloma. In addition to all of the above, the FLC ratio is required for documenting stringent complete response (sCR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.⁹ The FLC assay cannot replace the 24-hour UPEP for monitoring patients with measurable urinary M-protein. Once the myeloma or M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

Bone Marrow Evaluation: To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells.

Radiographic Evaluation: To evaluate lytic bone lesions, full skeleton radiographic survey or whole body low-dose CT is recommended.¹⁰⁻¹²

Cytogenetic Studies: Although MM may be morphologically similar, several subtypes of the disease have been identified at the genetic and molecular level. Bone marrow studies at initial diagnosis should include chromosome analysis by metaphase cytogenetics and fluorescence in situ hybridization (FISH) performed with the plasma cells obtained from bone marrow aspiration. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications.

Deletion of 17p13 (the locus for the tumor-suppressor gene, p53) leads to loss of heterozygosity of *TP53* and is considered a high-risk feature in MM.¹³⁻¹⁵ Other high-risk chromosomal aberrations in MM are characterized by structural changes that include specific rearrangements involving the *IGH* gene (encoding immunoglobulin heavy chain), located at 14q32. Several subgroups of patients are



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identified on the basis of 14q32 translocations. The main translocations are the t(11;14)(q13;q32), t(4;14)(p16;q32), t(14;16)(q32;q23), and t(14;20)(q32;q12). Several studies have confirmed that MM patients with t(4;14), t(14;16), and t(14;20) have a poor prognosis, while t(11;14) is believed to impart less risk.¹⁶⁻¹⁹ del(13q) is a common abnormality that is observed on FISH studies, but is a negative prognostic factor only when observed on metaphase cytogenetics.

Abnormalities of chromosome 1 are also among the frequent chromosomal alterations in MM.²⁰ The short arm is most often associated with deletions and the long arm with amplifications.²¹ Gains/amplification of 1q21 increases the risk of MM progression and incidence of the amplification is higher in relapsed than in newly diagnosed patients.^{20,22}

Stratification of patients into various risk groups based on the chromosomal markers is being utilized by some centers for prognostic counseling, selection, and sequencing of therapy approaches.^{23,24} According to the NCCN Multiple Myeloma Panel Members, the FISH panel for prognostic estimation of plasma cells should, at minimum, examine for t(4;14), t(14;16), 17p13 deletions, and chromosome 1 amplification. The utility of this information is to determine biological subtype and for prognostic recommendations.

Gene Expression Profiling: In addition to cytogenetic markers of prognosis, gene expression signatures may be capable of discerning prognosis and helping rational therapeutic decisions.^{25,26} Further understanding of the molecular subtypes of MM is emerging from the application of high-throughput genomic tools such as gene expression profiling (GEP).²⁷ With the currently available novel treatment approaches, a majority of patients with MM can now anticipate long-term disease control. However, patients with cytogenetically and

molecularly defined high-risk disease do not receive the same benefit from certain approaches as the low-risk patients and need alternative therapies. GEP is a powerful and fast tool with the potential to provide additional prognostic information to further refine risk stratification, help therapeutic decisions, and inform novel drug design and development. Several groups have identified and developed 15-gene, 70-gene, and 92-gene models based on GEP signatures of MM cells.²⁸⁻³⁰ Studies show that patients in the high-risk group based on the 15-gene,²⁸ 70-gene,²⁹ or 92-gene³⁰ models had shorter survival compared with the low-risk group. The NCCN Panel unanimously agreed that although GEP is not currently *routinely* used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.

Bone Marrow Immunohistochemistry and Flow Cytometry:

Immunohistochemistry and/or flow cytometry may be used to confirm presence of monoclonal plasma cells, and to more accurately quantify plasma cell involvement.³¹ The cytoplasm of abnormal plasma cells contain either kappa or lambda light chains, and predominance of one or the other light chain expressing plasma cells indicated clonality.

Additional Diagnostic Tests

The NCCN Multiple Myeloma Panel recommends additional tests that may be useful under some circumstances. These include whole body MRI³² or whole body PET/CT scan.¹² Active myeloma is positive on PET scan.^{33,34} PET/CT and MRI scans are more sensitive than plain radiographs and are indicated when symptomatic areas show no abnormality on routine radiographs. FDG PET/CT results after induction therapy and stem cell transplant help in predicting prognosis of patients with symptomatic MM.³⁵⁻³⁷

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell proliferation assays may be helpful to identify the fraction of proliferating myeloma cell population.³⁸ Also, if amyloidosis is suspected, the diagnosis is established by following the recommendations outlined in the NCCN Guidelines for Systemic Light Chain Amyloidosis.

Serum viscosity should be evaluated, particularly in those with high levels of M-protein.

In selected patients with MM, allogeneic transplantation may be considered. In this approach, myeloablative or non-myeloablative/reduced-intensity therapy is administered with infusion of stem cells (ie, peripheral blood or bone marrow) obtained from a donor, preferably a human leukocyte antigen (HLA)-identical sibling. In such cases, the patient will need to be HLA-typed.

Based on the results of the clinical and laboratory evaluation discussed in previous sections, patients are initially classified as either having smoldering (asymptomatic) disease or active (symptomatic) disease. For definitions refer to *Definition of Multiple Myeloma (Smoldering and Active)* in the algorithm.

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing requirements of CRAB features.³⁹ The CRAB criteria that define MM include: hypercalcemia [>11.5 mg/dL], renal insufficiency [creatinine >2 mg/dL or creatinine clearance <40 mL/min], anemia [hemoglobin <10 g/dL or 2 g/dL $<$ normal], and presence of bone lesions. The IMWG has also clarified that presence of one or more osteolytic lesions seen on skeletal radiography, whole body MRI, or whole body PET/CT fulfills the criteria for bone disease.³⁹ The MM-defining biomarkers identified by the IMWG include one or more of

the following: $\geq 60\%$ clonal plasma cells in the bone marrow; involved/uninvolved FLC ratio of 100 or more with the involved FLC being ≥ 100 mg/L; or MRI with more than one focal lesion (involving bone or bone marrow).³⁹

The criteria by the IMWG for smoldering (asymptomatic) patients include serum M-protein (IgG or IgA) ≥ 30 g/L and/or clonal bone marrow plasma cells 10% to 60% and absence of CRAB features, myeloma-defining events, or amyloidosis.³⁹ The updated IMWG diagnostic criteria for MM allow initiation of therapy before end-organ damage on the basis of specific biomarkers, and also allow the use of sensitive imaging criteria to diagnose MM, including PET/CT and MRI.³⁹

Those with active myeloma can be staged using either the Durie-Salmon Staging System or the International Staging System (ISS).⁴⁰ The ISS is based on easily obtained laboratory measures (serum beta-2 microglobulin and serum albumin) and is easier to use than the Durie-Salmon Staging System for patients with previously untreated MM. The ISS has been recently revised to incorporate the serum LDH and high-risk FISH abnormalities [t(4;14), t(14;16), 17p13 deletion].⁴¹

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment.

The updated IMWG response criteria definitions^{9,42,43} for complete response (CR), sCR, immunophenotypic CR, molecular CR, very good partial response (VGPR), partial response (PR), minimal response (MR) for relapsed/refractory myeloma, stable disease (SD), and progressive disease (PD) are outlined in *Response Criteria for Multiple Myeloma* in the algorithm. This has been recently updated to include measures of



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minimal residual disease (MRD) assessments. It is recommended that the IMWG uniform response criteria should be used in all clinical trials.⁴⁴

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a thorough evaluation to rule out the presence of additional lesions or systemic disease, because many patients presumed to have solitary plasmacytomas are found to have occult disease. Solitary plasmacytomas are further categorized as osseous or extraosseous. Osseous plasmacytoma is defined as a plasmacytoma emanating from bone without other evidence of disease. Solitary plasmacytomas derived from soft tissue are termed extraosseous.⁴⁵ An analysis of the SEER database between 1992 and 2004 found that incidence of osseous plasmacytoma was 40% higher than extraosseous plasmacytoma ($P < .0001$).⁴⁶

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for osseous and extraosseous plasmacytomas are similar. Radiation therapy has been shown to provide excellent local control of solitary plasmacytomas.⁴⁷⁻⁵³ The largest retrospective study (N = 258) included patients with solitary plasmacytoma (n = 206) or extramedullary plasmacytoma (n = 52).⁵⁴ Treatments included RT alone (n = 214), RT plus chemotherapy (n = 34), and surgery alone (n = 8). Five-year OS was 74%, disease-free survival was 50%, and local control was 85%. Patients who received localized RT had a lower rate of local relapse (12%) than those who did not (60%).⁵³

The optimal radiation dose for treatment of solitary plasmacytomas is not known. The dose used in most published papers ranges from 30 to 60 Gy.^{52,53,55}

For those patients with osseous plasmacytoma, the NCCN Panel recommends primary radiation therapy (40–50 Gy in 1.8–2.0 Gy/fraction) to the involved field followed by surgery if structurally unstable or if there are any issues related to neurologic compression. For extraosseous plasmacytomas primary treatment is radiation therapy (40–50 Gy in 1.8–2.0 Gy/fraction)⁵⁰ to the involved field followed by surgery,⁵⁶ if necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for both solitary plasmacytoma and extraosseous plasmacytoma consist of blood and urine tests. Serial and frequent measurements of M-protein are required to confirm disease sensitivity. The recommended follow-up interval for these patients is every 3 to 6 months; however, patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up.

The blood tests include CBC; serum chemistry for creatinine, albumin, and corrected calcium; serum quantitative immunoglobulins; and SPEP with SIFE as needed. Testing for serum FLC assay, LDH, and beta-2 microglobulin may be useful under some circumstances.

The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow aspirate and biopsy, and imaging studies using whole body MRI or low-dose CT or PET/CT are recommended as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.^{34,57,58} Skeletal survey is recommended annually or as clinically indicated.



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If progression to myeloma occurs, then the patient should be re-evaluated as described in the Discussion section, *Diagnosis and Workup*, and systemic therapy must be administered as clinically indicated.

Smoldering (Asymptomatic) Myeloma

Smoldering (asymptomatic) myeloma describes a stage of disease with no symptoms and no related organ or tissue impairment.⁵⁹ Patients with Durie-Salmon stage I myeloma with low amounts of M-protein without significant anemia, hypercalcemia, or bone disease would be included in this category. Patients with asymptomatic smoldering MM may have an indolent course for many years without therapy.

Primary Therapy for Smoldering (Asymptomatic) Myeloma

Patients with smoldering myeloma do not need primary therapy, as it may take many months to years before the disease progresses. The risk of transformation to symptomatic myeloma⁶⁰ in these patients is life-long and therefore should be followed closely.

A relatively small, randomized, prospective, phase III study by the PETHEMA group investigated whether early treatment with lenalidomide and dexamethasone in patients (n = 125) with smoldering myeloma, at high risk of progression to active MM, prolongs the time to progression.⁶¹ The high-risk group in the study was defined using the following criteria: plasma cell bone marrow infiltration of at least 10% and/or a monoclonal component (defined as an IgG level of ≥ 3 g/dL, an IgA level of ≥ 2 g/dL, or a urinary Bence Jones protein level of >1 g per 24 hours); and at least 95% phenotypically aberrant plasma cells in the bone marrow infiltrate. The OS reported in the trial at 3 years was higher in the group treated with the lenalidomide and dexamethasone arm (94% vs. 80%; HR, 0.31; 95% CI, 0.10–0.91; $P = .03$).⁶¹ At a

median follow-up of 75 months (range, 27–57 months), treatment with lenalidomide and dexamethasone delayed median time to progression to symptomatic disease compared to no treatment (time to progression was not reached in the treatment arm compared to 23 months in the observation arm; HR, 0.24; 95% CI, 0.14–0.41).⁶² The high OS rate seen after 3 years was also maintained (HR, 0.43; 95% CI, 0.20–0.90).

According to the NCCN Panel, the flow cytometry-based high-risk criteria specified in the study is not uniformly available. Based on the criteria used in the trial, some patients with active myeloma were classified as having high-risk smoldering myeloma. The NCCN Panel strongly believes there is need to re-evaluate the definition of high-risk smoldering myeloma. The panel believes that it is too early to begin treating *all* patients with smoldering myeloma at high risk (as defined in the trial) of progression to active MM with any anti-myeloma therapy. The NCCN Multiple Myeloma Panel recommends that patients with smoldering myeloma should initially be observed at 3- to 6-month intervals (category 1 recommendation) or strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.

Surveillance/Follow-up Tests for Smoldering (Asymptomatic) Myeloma

The surveillance/follow-up tests include CBC; serum chemistry for creatinine, albumin, corrected calcium, serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay as clinically indicated. The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Skeletal survey or whole body low-dose CT is recommended as clinically indicated. Bone marrow aspiration and biopsy and imaging studies with MRI and/or CT and/or PET/CT are recommended as clinically indicated.⁶³ PET imaging seems to reliably predict active



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myeloma; by virtue of FDG uptake, low-level smoldering myeloma is typically negative on the PET scan.³³ It can also assess the extent of active disease, detect extramedullary involvement, or evaluate treatment response.^{34,64-66}

Multiparameter flow cytometry is a newly available tool that can help individualize the follow-up/surveillance strategy for patients with smoldering myeloma. It measures abnormal cells in the bone marrow and provides information regarding the risk of progression to active myeloma. A high proportion of abnormal plasma cells within the bone marrow plasma cell compartment (>95%) has been shown to predict the risk of progression in patients with smoldering myeloma or MGUS, as has quantity and type of M-protein (non-IgG) and abnormal serum FLC assay.^{67,68} According to the NCCN Multiple Myeloma Panel Members, multiple parameter flow cytometry information may be a useful consideration in the follow-up/surveillance plan of patients with smoldering myeloma. Since this test is not standardized or widely available, they recommend that it should only be performed in laboratories with experience.

If the disease progresses to symptomatic myeloma, then patients should be treated according to the guidelines for symptomatic MM.

Active (Symptomatic) Multiple Myeloma

Primary Therapy for Active (Symptomatic) Multiple Myeloma

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients, primary therapy is followed by high-dose chemotherapy with autologous stem cell transplant (SCT). Research into various primary regimens has focused on improving the response rates and depth of response in both transplant and non-transplant candidates. The NCCN Panel Members

have noted that it is important to assess for response to primary therapy after every cycle of therapy.

Stem cell toxins, such as nitrosoureas or alkylating agents, may compromise stem cell reserve, and regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for SCT. Therefore, one of the first steps in evaluating patients with advanced MM is to determine whether they are candidates for high-dose therapy and transplant, based on age and comorbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. Therefore, referral to a stem cell center to assess stem cell candidacy is important.

It is also important to consider supportive care for all patients at diagnosis. For example, 80% of patients have bone disease and up to 33% have renal compromise. PI-based regimens may be of value in patients with renal failure, and in those with certain adverse cytogenetic features.⁶⁹

Bone disease, renal dysfunction, and other complications such as hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see *Supportive Care Treatment for Multiple Myeloma* in this Discussion). In all patients, careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

The page titled *Myeloma Therapy* in the guidelines has a list of primary therapy regimens recommended by the NCCN Multiple Myeloma Panel members for transplant and non-transplant candidates and also lists drugs recommended for maintenance therapy. The list is selected and is not inclusive of all regimens. The NCCN Multiple Myeloma Panel has



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categorized all myeloma therapy regimens as: “preferred,” “other recommended,” or “useful under certain circumstances.”

The purpose of classifying regimens as such is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens. Factors considered by the panel include evidence, efficacy, toxicity, pre-existing comorbidities such as renal insufficiency, and in some cases access to certain agents.

The NCCN panel prefers 3-drug regimens over 2-drug regimens as the standard of care for primary treatment of myeloma. This is based on improved response rates, depth of response, and rates of progression-free survival (PFS) or overall survival (OS) seen with 3-drug regimens in clinical trials. However, the panel notes that doublets could be used if a patient is elderly and/or frail and unable to tolerate a 3-drug regimen.

Prophylaxis with full-dose aspirin is recommended for those receiving an IMiD-based therapy. An anticoagulation agent is recommended for patients receiving an IMiD-based therapy and who are at high risk for thrombosis.

Prophylactic antiviral therapy is recommended for all patients receiving PI-based therapies.^{70,71} This is because impaired lymphocyte function that results from MM and/or its treatment-related myelosuppression may lead to reactivation of herpes simplex infection or herpes zoster.⁷¹⁻⁷⁴

Carfilzomib can potentially cause cardiac and pulmonary toxicities.⁷⁵ Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended.⁷⁵

Preferred Primary Therapy Regimens for Transplant Candidates

Bortezomib-based 3-drug regimens have been listed as preferred primary therapy options for patients who are SCT eligible. These

include bortezomib/lenalidomide/dexamethasone, bortezomib/doxorubicin/dexamethasone, and bortezomib/cyclophosphamide/dexamethasone.

The NCCN panel has noted that subcutaneous administration is the preferred route for bortezomib. This is based on the results of the MMY-3021 trial. The trial randomized 222 patients to single-agent bortezomib administered either by the conventional intravenous (IV) route or by subcutaneous route.⁷⁶ The findings from the study demonstrate non-inferior efficacy with subcutaneous versus IV bortezomib with regard to the primary endpoint (overall response rate [ORR] after 4 cycles of single-agent bortezomib). Consistent results were shown with regard to secondary endpoints.⁷⁶ The results showed no significant differences in terms of time to progression or in one-year OS between groups.^{76,77} However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy. The panel recommends herpes prophylaxis in patients receiving bortezomib therapy.

The NCCN Multiple Myeloma Panel recommends harvesting peripheral blood stem cells early in the course of primary treatment, preferably after 3 to 4 cycles of initial therapy.

Bortezomib/Lenalidomide/Dexamethasone

Phase II and III studies results have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in all newly diagnosed patients with MM, transplant eligible as well as transplant ineligible.⁷⁸⁻⁸⁰

In the first phase I/II prospective study of lenalidomide/bortezomib/dexamethasone in patients with newly diagnosed MM, the rate of partial response was 100%, with 74% VGPR or better and 52% CR/near CR.⁷⁸ The benefits of



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bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial⁸⁰ and phase II EVOLUTION trial.⁷⁹ In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by SCT.⁸⁰ Patients subsequently received two cycles of bortezomib/lenalidomide/dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. VGPR rate or better at the completion of induction was 58%.⁸⁰ After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.⁸⁰ The phase II EVOLUTION trial was designed to examine the tolerability and efficacy of combining bortezomib/cyclophosphamide/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone versus bortezomib/cyclophosphamide/dexamethasone in a randomized multicenter setting.⁷⁹ The ORR after primary treatment with bortezomib/lenalidomide/dexamethasone followed by maintenance with bortezomib was 85% (51% ≥ VGPR and 24% CR) and corresponding one-year PFS was 83% in the bortezomib/lenalidomide/dexamethasone arm.⁷⁹

This triplet was compared to lenalidomide/dexamethasone in the multicenter phase III SWOG S077 trial.⁸¹ Patients (n = 525) with previously untreated MM were randomly assigned to receive 6 months of induction therapy with either bortezomib/lenalidomide/dexamethasone (N = 264) or lenalidomide/dexamethasone (N = 261), each followed by maintenance therapy with lenalidomide/dexamethasone until progression or unacceptable. The triple-drug regimen group had significantly longer PFS (43 months vs. 30 months; HR, 0.712; 96% CI, 0.56–0.906) and improved median OS (75 months vs. 64 months; HR, 0.709; 95% CI, 0.524–0.959).⁸¹ As expected, ≥ Grade 3 neuropathy was more frequent

in the bortezomib-containing arm (24% vs. 5%; $P < .0001$) as bortezomib was administered intravenously in this study.⁸¹

Based on the significant improvement in PFS and OS seen with bortezomib/lenalidomide/dexamethasone, the NCCN panel included this regimen as a category 1, preferred option for primary treatment of transplant-eligible patients with MM.

Bortezomib/Cyclophosphamide/Dexamethasone

Data from 3 phase II studies involving newly diagnosed patients with MM have demonstrated high response rates with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) as primary treatment.^{79,82,83}

The trial by Reeder et al carried out in the United States and Canada demonstrated an ORR of 88% including a VGPR or greater of 61% and 39% CR/near CR with CyBorD as the primary regimen.⁸² The depth of response seen after primary treatment was maintained after transplant in those who underwent transplantation (70% rates of CR/near CR; rate of at least VGPR or better was 74%).⁸² According to the long-term follow-up analysis, the 5-year PFS and OS rates were 42% (95% CI, 31–57) and 70% (95% CI, 59–82).⁸⁴

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR was 84%, with 74% PR rate and 10% CR rate). High response rates were seen in patients with unfavorable cytogenetics.⁸³

In the updated results of the phase II EVOLUTION study, primary treatment with CyBorD demonstrated an ORR of 75% (22% CR and 41% ≥VGPR), and the one-year PFS rate was 93%.⁷⁹

Based on data from these and other phase II studies, the NCCN Multiple Myeloma Panel has now included the combination of cyclophosphamide/bortezomib/dexamethasone to the list of primary



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treatment available for transplant candidates. This is a preferred option, especially in patients with acute renal insufficiency. According to the NCCN panel, one can consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

Twice-weekly bortezomib can be associated with toxicities that may limit efficacy caused by treatment delays or discontinuation. Therefore, Reeder et al modified the regimen to a once-weekly schedule of bortezomib.⁸⁵ In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (ORR 93% vs. 88%, VGPR 60% vs. 61%). In addition, they experienced less grade 3/4 adverse events (37%/3% vs. 48%/12%). Fewer dose reductions of bortezomib/dexamethasone were required in the modified schedule and neuropathy rates were the same in both cohorts, even though the total bortezomib dose per cycle was higher in the weekly versus the twice-weekly schedule (6.0 mg/m² vs. 5.2 mg/m²).⁸⁵

Other Recommended Primary Therapy Regimens for Transplant Candidates

Bortezomib/Doxorubicin/Dexamethasone

The updated results from the HOVON-65/GMMG-HD4 group phase III trial of newly diagnosed patients with stage II/III MM demonstrated high response rates after primary therapy with bortezomib/doxorubicin/dexamethasone versus vincristine/doxorubicin/dexamethasone (VAD), and this superior response rate (CR + near CR was 31% vs. 15%; $P < .001$) was maintained even after SCT with significantly higher ORR.⁸⁶ No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs. 49%; $P < .001$).⁸⁶ After a median follow-up of 41 months, PFS in patients treated with bortezomib/doxorubicin/dexamethasone as primary therapy followed by

SCT and bortezomib maintenance was 35 months versus 28 months in patients treated with VAD followed by SCT and maintenance with thalidomide. Patients treated with bortezomib/doxorubicin/dexamethasone had a significantly better PFS (HR, 0.75; 95% CI, 0.62–0.90; $P = .002$).⁸⁶ The OS was also found to be better in the bortezomib, doxorubicin, and dexamethasone arm (HR, 0.77; 95% CI, 0.60–1.00; $P = .049$). In high-risk patients presenting with increased creatinine more than 2 mg/dL, bortezomib significantly improved PFS from a median of 13 months to 30 months (HR, 0.45; 95% CI, 0.26–0.78; $P = .004$) and OS from a median of 21 months to 54 months (HR, 0.33; 95% CI, 0.16–0.65; $P < .001$). A benefit in terms of increased PFS was also observed in patients with deletion of 17p13.⁸⁶ The rate of grade 2 to 4 peripheral neuropathy was higher in those treated with the bortezomib-containing regimen versus VAD (40% vs. 18%). In addition, newly developed grade 3 to 4 peripheral neuropathy occurred in 8% of patients during thalidomide maintenance and 5% of patients during bortezomib maintenance.⁸⁶

Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/doxorubicin/dexamethasone is a category 1 option for primary therapy for transplant-eligible patients with MM.

Carfilzomib/Lenalidomide/Dexamethasone

Carfilzomib is a second-generation PI that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. Preclinical studies with carfilzomib show lack of neurodegeneration in vitro⁸⁷ and less neurotoxicity in animal studies.⁸⁸ Carfilzomib has demonstrated anti-myeloma activity in patients with relapsed and/or refractory MM with an acceptable tolerability profile, including limited neuropathy after prolonged treatment.⁸⁹⁻⁹¹



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The safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone, as *primary* therapy for patients with MM, were evaluated in two single-arm trials.

First, a multicenter phase I/II trial evaluated the combination of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM.⁹² In this trial, patients (n = 53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, stem cells were collected from eligible patients.⁹² Out of 35 patients from whom stem cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.⁹² With median follow-up of 13 months, 24-month PFS was estimated at 92%. The most common grade 3 and 4 toxicities in ≥10% of patients included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%). Peripheral neuropathy was limited to grade 1/2 (23%).⁹²

Another phase II trial also evaluated the same regimen (carfilzomib in combination with lenalidomide and dexamethasone) in newly diagnosed patients (n = 45) with MM. After 8 cycles of treatment, patients with SD received up to 24 cycles of lenalidomide 10 mg/d on days 1 to 21.⁹³ Thirty-eight patients were evaluable for response and toxicity. After a median follow-up of 10 months, PFS was 83.3%. Twenty-five patients completed 8 cycles of the carfilzomib, lenalidomide, and dexamethasone regimen, of which 24 continued to lenalidomide therapy and 1 patient opted to exit the study after initial therapy. The most common non-hematologic and hematologic toxicities (≥ grade 3) in >10% of patients included electrolyte disturbances (18%), liver function test elevation (13%), rash/pruritus (11%), fatigue (11%), lymphopenia (63%), anemia (16%), leukopenia (13%), and thrombocytopenia (11%).⁹⁴

The results of a phase 2 trial multicenter study of carfilzomib/lenalidomide/dexamethasone in newly diagnosed transplant-eligible patients (n = 76) showed that CR or better was seen in 86% of patients at the end of 18 cycles for carfilzomib/lenalidomide/dexamethasone plus autologous SCT compared to 59% for carfilzomib/lenalidomide/dexamethasone and no autologous SCT. The 3-year PFS was 80% for carfilzomib/lenalidomide/dexamethasone alone and 86% for carfilzomib/lenalidomide/dexamethasone with autologous SCT patients. The 3-year OS was 96% for carfilzomib/lenalidomide/dexamethasone alone and 95% for carfilzomib/lenalidomide/dexamethasone with autologous SCT. The grade ≥ 3 adverse events, with autologous SCT versus autologous SCT, included lymphopenia (25% vs. 45%), neutropenia (25% vs. 30%), and infection (16% vs. 8%). In the carfilzomib/lenalidomide/dexamethasone with autologous SCT, the cardiac adverse events were 4% for all grades (0% grade 3/4), hypertension was 16% (4% grade 3/4), and dyspnea was 32% (3% grade 3/4).⁹⁵

Based on the data from the above phase II studies, the NCCN panel has included the carfilzomib, lenalidomide, and dexamethasone regimen as an option for primary treatment of transplant-eligible patients with MM. A phase III trial by the ECOG-ACRIN Cancer Research Group comparing carfilzomib/lenalidomide/dexamethasone to bortezomib/lenalidomide/dexamethasone is currently recruiting patients (Clinical Trial ID: NCT01863550). The NCCN panel strongly encourages participation in clinical trial.

Ixazomib/Lenalidomide/Dexamethasone

Ixazomib is an oral PI that was approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy.

In a phase I/II trial, Kumar et al studied an all-oral combination of ixazomib/lenalidomide/dexamethasone in patients with newly diagnosed MM.⁹⁶ The results of this trial show that the regimen was well tolerated and active in the study population. Out of the 64 patients in whom the response could be evaluated, 37 (58%; 95% CI, 45–70) had a VGPR or better. Grade 3 or higher adverse events related to any drug in the combination were reported in 41 (63%) patients. These included skin and subcutaneous tissue disorders (11 patients, 17%), neutropenia (8 patients, 12%), and thrombocytopenia (5 patients, 8%); drug-related peripheral neuropathy of grade 3 or higher occurred in 4 (6%) patients.

Based on these phase II results and the fact that the combination of other PIs (bortezomib or carfilzomib) in combination with lenalidomide/dexamethasone have been shown to be as effective as primary therapy in newly diagnosed MM,^{81,92-94,97} the NCCN panel has included ixazomib/lenalidomide/dexamethasone as an option (category 2B) for treatment of patients with newly diagnosed MM. An ongoing phase III trial is evaluating ixazomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone (Clinical trial ID: NCT01850524).

Regimens Useful Under Certain Circumstances for Transplant Candidates

While triple-drug regimens remain the preferred primary therapy option for patients with MM, selected patients such as those who are elderly or frail may be initially treated with regimens containing two drugs such as bortezomib/dexamethasone or lenalidomide/dexamethasone; a third drug could be added when the patient's condition improves.

Bortezomib/Dexamethasone

In the IFM cooperative group trial, 482 patients eligible for transplant were randomized to one of the following 4 primary therapy arms: VAD (n = 121) alone; VAD plus consolidation therapy with

dexamethasone/cyclophosphamide, etoposide/cisplatin (DCEP; n = 121); bortezomib/dexamethasone (n = 121); or bortezomib/dexamethasone plus consolidation with DCEP (n = 119).⁹⁸ The primary endpoint was assessing response rate after primary therapy. The investigators evaluated the response according to modified European Group for Blood and Marrow Transplantation (EBMT) criteria,⁹⁹ including additional categories of near CR (CR but immunofixation-positive)¹⁰⁰ and VGPR (serum M-protein reduction $\geq 90\%$; urine light chain < 100 mg/24 hours).⁹ After primary therapy, the ORR (78.5% vs. 62.8%) and the rates of CR/near CR (14.8% vs. 6.4%) and VGPR (37.7% vs. 15.1%) were significantly higher with bortezomib/dexamethasone versus VAD.⁹⁸ At a median follow-up of 32.2 months, median PFS was modestly but not statistically significantly prolonged compared to VAD (36.0 months vs. 29.7 months).⁹⁸ Use of DCEP as consolidation therapy after primary therapy did not have a significant impact on the rates of response.⁹⁸ The bortezomib/dexamethasone regimen was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities. The incidence of severe adverse events reported was similar between the two groups. Hematologic toxicity and deaths related to toxicity were more frequent with VAD versus bortezomib/dexamethasone. The rates of grade 2 (20.5% vs. 10.5%) and grades 3 to 4 (9.2% vs. 2.5%) peripheral neuropathy during induction through first transplantation were significantly higher with bortezomib/dexamethasone compared to VAD.⁹⁸

The IFM conducted a phase III randomized trial comparing bortezomib/dexamethasone with a combination of reduced doses of bortezomib and thalidomide plus dexamethasone.¹⁰¹ The response rates achieved in the comparing bortezomib/dexamethasone arm seen



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in this study match those described in previous trials comparing VAD with bortezomib and dexamethasone.⁹⁸

Patients with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and OS. A study analyzed a large series of patients (younger 65 years) with newly diagnosed transplant-eligible MM treated and t(4;14) or del(17p) treated with bortezomib/dexamethasone versus VAD as primary therapy before treatment.⁶⁹ The analysis demonstrated that bortezomib improves the prognosis (in terms of both EFS and OS; $P < .001$ and $P < .001$, respectively) of patients with t(4;14) compared with patients treated with VAD primary therapy.⁶⁹

Based on these data and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/dexamethasone is listed as a category 1 primary therapy option for transplant-eligible patients with MM under the category “useful under certain circumstances” because, as mentioned above, triple-drug regimens are preferred as primary therapy for transplant-eligible patients with MM. However, those with comorbid conditions such as with renal insufficiency may be treated with the bortezomib/dexamethasone doublet initially and a third drug could be added when renal insufficiency or overall condition improves.

Lenalidomide/Dexamethasone

Lenalidomide is a potent analogue of thalidomide. Like thalidomide, it is believed to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis and inhibition of angiogenesis and cytokine circuits, among others. Lenalidomide received approval from the U.S. Food and Drug Administration (FDA) for the treatment of relapsed/refractory MM in combination with dexamethasone.

Lenalidomide and dexamethasone have also been investigated as primary therapy. The phase III randomized controlled study, S0232, by Southwest Oncology Group (SWOG) compared dexamethasone single

agent with dexamethasone plus lenalidomide for patients newly diagnosed with MM.¹⁰² This trial was halted at interim analysis and patients on dexamethasone alone were allowed to switch to lenalidomide/dexamethasone. The SWOG data and safety monitoring committee based its recommendation to permanently close enrollment based on the preliminary results from the ECOG phase III study (E4A03).¹⁰³ At the time the SWOG trial was halted, at the end of one year, the lenalidomide plus dexamethasone arm showed improved CR rate compared to dexamethasone alone (22.1% vs. 3.8%).¹⁰²

E4A03 was an open-label trial, with 445 newly diagnosed patients with MM randomly assigned to high-dose or low-dose dexamethasone regimens. The response was superior with high-dose dexamethasone. One hundred sixty-nine (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients receiving low-dose therapy had CR or PR within 4 cycles.¹⁰⁴ However, the high response rates did not result in superior time to progression, PFS, or OS compared with low-dose dexamethasone. The trial was stopped early and patients on high-dose therapy were allowed to cross over to the low-dose arm since the OS rate was significantly higher in that arm. At 1-year interim analysis, OS was 96% in the low-dose dexamethasone group compared with 87% in the high-dose group ($P = .0002$); 2-year OS was 87% versus 75%, respectively.

The cause of inferior OS with high-dose dexamethasone seems to be related to increased deaths caused by toxicity. Fifty-two percent of patients on the high-dose regimen compared with 35% on the low-dose regimen had grade 3 or worse toxic effects in the first 4 months, including deep vein thrombosis (DVT) (26% vs. 12%); infections including pneumonia (16 vs. 9%); and fatigue (15% vs. 9%). The 3-year OS of patients who received 4 cycles of primary treatment with either dose followed by autologous SCT was 92%, suggesting that



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lenalidomide and dexamethasone is a reasonable choice for primary therapy before SCT. However, it should be noted that the choice to proceed to SCT was not randomized but based on physician and patient preference.

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but risk rises when combined with high-dose dexamethasone. According to a recent report, patients treated with lenalidomide and high-dose dexamethasone that developed a venous thromboembolism (VTE) did not experience shorter OS or time to progression.¹⁰⁵ Prophylactic anticoagulation is recommended in patients receiving this therapy.^{70,106}

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported.^{107,108} Guidelines by the IMWG suggest that patients treated with lenalidomide and dexamethasone should have stem cells collected within the first 4 cycles of therapy.¹⁰⁹ This inability to collect stem cells may be overcome by chemo-mobilization.¹¹⁰ Addition of plerixafor can also allow stem cell mobilization when conventional mobilization methods fail.^{111,112}

Lenalidomide/dexamethasone is listed as a category 1 primary treatment option in the NCCN Guidelines under the category “useful under certain circumstances,” noting that triple-drug regimens are preferred as primary therapy for transplant-eligible patients with MM. However, elderly or frail patients may be treated with doublet regimens. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Bortezomib/Thalidomide/Dexamethasone

Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and

cytokine circuits, among others. The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib/thalidomide/dexamethasone (N = 241) versus thalidomide/dexamethasone (N = 239) as primary therapy, followed by tandem autologous SCT with high-dose melphalan and then consolidation therapy with the same primary regimen.¹¹³ The addition of bortezomib to thalidomide and dexamethasone significantly improved ORR after primary treatment. After primary therapy, CR/near CR was achieved in 73 patients (31%; 95% CI, 25.0–36.8) receiving bortezomib/thalidomide/dexamethasone, and 27 patients (11%; 95% CI, 7.3–15.4) receiving thalidomide/dexamethasone.¹¹³ Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib/thalidomide/dexamethasone group than in the thalidomide/dexamethasone group after the first and second autologous SCT and subsequent consolidation therapy.¹¹³ Patients receiving the bortezomib-containing regimen experienced grade 3/4 peripheral neuropathy.

Data from a single-institution retrospective study are similar to the interim data from the GIMEMA trial.¹¹⁴ The findings of this analysis demonstrate that ORR after primary therapy with bortezomib/thalidomide/dexamethasone was 94% of the patients (32 of 34 patients showed some response, including a VGPR rate ≥56%).¹¹⁴

The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) also demonstrated a significantly higher CR rate with bortezomib/thalidomide/dexamethasone as primary therapy overall (35% vs. 14%, $P = .001$) and in patients with high-risk cytogenetics (35% vs. 0%, $P = .002$).¹¹⁵ The CR rate continued to be significantly higher after autologous SCT (46% vs. 24%) in patients treated with bortezomib/thalidomide/dexamethasone versus thalidomide/dexamethasone as primary therapy.¹¹⁵



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The phase III IFM 2013-04 trial is evaluating 4 cycles of CyBorD versus 4 cycles of bortezomib/thalidomide/dexamethasone as induction therapy before autologous SCT in patients (N = 340) with newly diagnosed MM.¹¹⁶ The results reported during the 2015 ASH meeting show that patients who received bortezomib/thalidomide/dexamethasone as induction therapy achieved higher ORR (92.3%) compared with those who received CyBorD (84%). Those who received bortezomib/thalidomide/dexamethasone had significantly greater VGPR ($P = .04$) and PR ($P = .02$) rates.¹¹⁶ The hematologic toxicity was greater in the CyBorD arm; however, higher rates of peripheral neuropathy were reported in the bortezomib/thalidomide/dexamethasone arm.¹¹⁶

No significant difference in OS was observed in any of the trials with bortezomib/thalidomide/dexamethasone. A longer follow-up period is required. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Bortezomib/thalidomide/dexamethasone is listed as a primary treatment option (category 1) under the category “useful under certain circumstances.” Thalidomide is not widely used in the United States; however, it is more easily available and affordable in other resource-constrained parts of the world.

Bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE)

The total therapy 3 (TT3) trial evaluated induction therapy with the multi-agent regimen, VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) prior to high-dose melphalan-based tandem auto-transplants and later as consolidation therapy.¹¹⁷ This regimen is a potent combination of new agents as well as traditional chemotherapy agents.

This regimen is listed under the category “useful under certain circumstances.” According to the NCCN panel, VTD-PACE could be an option for newly diagnosed patients presenting with high risk and aggressive extramedullary disease or plasma cell leukemia.

Preferred Primary Therapy Regimens for Non-Transplant Candidates

Many of the regimens described above for transplant candidates are also options for non-transplant candidates. As in transplant-eligible patients, 3-drug regimens are preferred by the NCCN panel as these regimens have shown to induce higher response rates and depth of response in clinical trials. The 2-drug regimens are reserved for elderly and/or frail patients. The list of preferred options for non-transplant candidates includes: bortezomib/cyclophosphamide/dexamethasone, bortezomib/lenalidomide/dexamethasone, and lenalidomide/low-dose dexamethasone. Melphalan-containing regimens are no longer considered the standard of care in this setting since novel agents are available and accessible to patients in the United States.

Bortezomib/Lenalidomide/Dexamethasone

Phase II study results (discussed in the transplant setting) have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in all newly diagnosed patients with MM regardless of autologous SCT status.⁷⁸

The randomized phase III SWOG S0777 trial (discussed in the transplant setting), comparing bortezomib/lenalidomide/dexamethasone to lenalidomide/dexamethasone as induction therapy without an intent of immediate transplantation, reported superior results with the 3-drug regimen.⁸¹ The NCCN panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1, preferred option for patients with MM not eligible for SCT.

Lenalidomide/Low-dose Dexamethasone

The results of the SWOG SO232 trial¹⁰² that included transplant-ineligible patients and the ECOG E4A03 trial¹¹⁸ that included elderly patients with MM demonstrate that lenalidomide in combination with low-dose dexamethasone is a well-tolerated and effective regimen for these groups of patients. In the ECOG E4A03 trial the OS rate was significantly higher in the lenalidomide plus low-dose dexamethasone arm compared with the lenalidomide plus high-dose dexamethasone arm (also discussed under *Preferred Primary Therapy Regimens for Transplant Candidates*).¹⁰⁴ The inferior survival outcome seen with high-dose dexamethasone was greatest in patients aged 65 years and older. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low-dose dexamethasone.¹⁰⁴

The international, multicenter trial (FIRST trial) evaluated efficacy and safety of lenalidomide/dexamethasone given continuously or for 72 weeks with melphalan/prednisone/thalidomide (MPT) in elderly (n = 1623) transplantation-ineligible patients with newly diagnosed MM.¹¹⁹ The primary endpoint of this trial was PFS, and secondary endpoints were OS and adverse events, including the incidence of secondary malignancies. After a median of 37 months of follow-up, the risk of progression or death was reduced by 28% in patients receiving continuous lenalidomide/dexamethasone versus MPT (HR, 0.72; 95% CI, 0.61–0.85, $P < .001$).¹¹⁹ Continuous lenalidomide/dexamethasone also reduced the risk of progression or death compared with 18 cycles of lenalidomide/dexamethasone (HR, 0.70; 95% CI, 0.89–1.20; $P = .70$). In the interim analysis, an OS benefit was seen in the lenalidomide/dexamethasone arm versus MPT (HR, 0.78; CI, 0.64–0.96, $P = .02$).¹¹⁹

There are several reports showing higher incidences of secondary malignancies when lenalidomide is used as a maintenance therapy post-transplantation or in a melphalan-containing regimen.¹²⁰⁻¹²³ In the FIRST trial, the overall incidence of secondary malignancies, including hematologic malignancies, was lower in the continuous lenalidomide/dexamethasone arm. The overall rates of second primary cancers were 3.0% in the continuous lenalidomide/dexamethasone arm, 6.0% in the arm receiving 18 cycles of lenalidomide/dexamethasone, and 5.0% in the MPT arm.¹¹⁹ In an analysis based on renal function of patients enrolled in the FIRST trial, continuous lenalidomide/low-dose dexamethasone compared with MPT reduced the risk of progression or death in patients with normal, mild, and moderate renal impairment by 33%, 30%, and 35%, respectively.¹²⁴

Lenalidomide/low-dose dexamethasone is considered a category 1, preferred option by the NCCN Multiple Myeloma Panel for transplant-ineligible patients with MM, especially the frail or elderly patients with standard-risk features. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial,^{119,125} the NCCN panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Bortezomib/Cyclophosphamide/Dexamethasone

The role of bortezomib/cyclophosphamide/dexamethasone as initial therapy for patients with MM ineligible for SCT was studied in a small phase II trial (n = 20).¹²⁶ The median age of patients in this study was 76 years (range 66–90). After a median of 5 cycles, the ORR was 95% with 70% of patients achieving VGPR or better response. With respect to toxicity, 6 patients experienced non-hematologic grade 3/4 adverse events (20%), including muscle weakness, sepsis, and pneumonia. Neutropenia and thrombocytopenia were seen in 2 patients (10%).¹²⁶



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Based on the above *and* the results from the EVOLUTION trial⁷⁹ (described earlier) that had included transplant-ineligible patients and the above phase II trial results,¹²⁶ the NCCN panel has included bortezomib/cyclophosphamide/dexamethasone as a preferred option for non-transplant candidates. This is a preferred option especially in patients with acute renal insufficiency. According to the NCCN panel, one can consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

Other Recommended Primary Therapy Regimens for Non-Transplant Candidates

Carfilzomib/Lenalidomide/Dexamethasone

The results of a phase I/II trial demonstrated that the combination of carfilzomib/lenalidomide/dexamethasone is well-tolerated and is also effective in all newly diagnosed patients.⁹² An updated follow-up analysis of the subset of 23 elderly patients (age ≥65 years) showed that use of the carfilzomib, lenalidomide, and low-dose dexamethasone regimen for an extended period of time resulted in deep and durable responses. All patients achieved at least a PR and with a median follow-up of 30.5 months. PFS rate reported was 79.6% (95% CI: 53.5–92.0) and OS was 100%.⁹⁷

The phase II trial by Korde et al⁹⁴ also showed that treatment with the carfilzomib/lenalidomide/dexamethasone regimen results in high rates of deep remission. The results were very similar across age groups, with the oldest patient on the trial being 88 years of age,⁹⁴ and the regimen was found to be effective in individuals with high-risk disease.¹²⁷

Based on the above phase II studies that did not exclude transplant-ineligible patients, the NCCN panel has included carfilzomib/

lenalidomide/dexamethasone as an option for treatment of all patients with newly diagnosed MM, including those who are not eligible for SCT.

Carfilzomib/Cyclophosphamide/Dexamethasone

A phase II study examined the safety and efficacy of carfilzomib/cyclophosphamide/dexamethasone in patients ≥65 years of age with newly diagnosed MM and ineligible for autologous SCT.¹²⁸ Out of 55 patients, 52 (95%) had at least a PR, 39 of 55 (71%) patients had at least a VGPR, 27 of 55 (49%) patients had a near CR or CR, and 11 of 55 (20%) patients had an sCR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively.¹²⁸ Frequently reported grade 3 to 5 toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary events (7%). Peripheral neuropathy was limited to grades 1 and 2 (9%).

The NCCN panel has included carfilzomib/cyclophosphamide/dexamethasone as an option for treatment of all patients with newly diagnosed MM not eligible for SCT.

Ixazomib/Lenalidomide/Dexamethasone

A phase I/II study (discussed in the previous section for SCT-eligible candidates) evaluated the safety and efficacy of the all-oral combination of ixazomib with lenalidomide and dexamethasone in patients with newly diagnosed MM treated with combination lenalidomide and dexamethasone.⁹⁶ Both tolerability and activity of this regimen in older patients (those aged 65 years and older) was similar to that in younger patients in this study.

Based on the above phase II study, the NCCN panel has included ixazomib in combination with lenalidomide and dexamethasone as a primary treatment option for all patients with newly diagnosed MM, including those *not* eligible for SCT.



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Regimens Useful Under Certain Circumstances for Non-Transplant Candidates

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter phase IIIb, UPFRONT trial compared safety and efficacy of 3 highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for SCT.¹²⁹ The patients with symptomatic, measurable MM were randomized (1:1:1) to one of the following regimens:

bortezomib/dexamethasone (n = 168);

bortezomib/thalidomide/dexamethasone (n = 167); or

melphalan/prednisone/bortezomib (n = 167) followed by maintenance therapy with bortezomib. The primary endpoint was PFS; secondary endpoints included ORR, CR/near-CR and VGPR rates, OS, and safety.

All 3 induction regimens exhibited substantial activity, with ORR of 73% (bortezomib/dexamethasone), 80%

(bortezomib/thalidomide/dexamethasone), and 69%

(melphalan/prednisone/bortezomib) during the treatment period.¹²⁹ After a median follow-up of 21.8 months, no significant difference in PFS was observed between the treatment arms.¹²⁹ Response rates, including CR and ≥VGPR, improved after bortezomib maintenance, with no concomitant increase in the incidence of peripheral neuropathy.

While the triple regimen with bortezomib/lenalidomide/dexamethasone is the preferred therapy for patients with newly diagnosed MM, elderly or frail patients may be treated with doublet regimens. The NCCN Multiple Myeloma Panel has included bortezomib/dexamethasone as a primary therapy as an option that is useful under certain circumstances for patients with MM who are ineligible for SCT.

Monitoring After Primary Myeloma Therapy of Both Transplant and Non-Transplant Candidates

Patients on treatment should be monitored for response to therapy, and for symptoms related to disease and/or treatment. It is recommended to re-evaluate (after 1–2 cycles) with the laboratory tests for M-protein (with imaging and bone marrow examination if indicated), to determine treatment response or whether the primary disease is progressive.

Potential transplant candidates should undergo a stem cell harvest after 4 to 6 cycles of therapy, collecting enough stem cells for two transplants (depending on the intended number of transplants and age) in anticipation of a tandem transplant or a second transplant as subsequent therapy. Alternatively, all patients may consider continuation of primary therapy until the best response is reached. The optimal duration of primary therapy after achieving maximal response is unknown; hence, maintenance therapy (see section on *Maintenance Therapy*) or observation can be considered beyond maximal response.

Follow-up tests after primary myeloma therapy include those used for initial diagnosis: a CBC with differential and platelet counts; serum creatinine and corrected serum calcium; and quantification of M-protein and immunoglobulins. The serum FLC may be assessed as clinically indicated (especially in patients with oligo- or non-secretory MM).

According to the NCCN panel, response should be assessed using the IMWG criteria.⁹ Other tests such as skeletal survey, whole body low-dose CT, bone marrow aspiration and biopsy, skeletal MRI, and PET/CT scan may be performed as indicated by symptoms to detect disease progression. Patients eligible for SCT should be referred for evaluation by SCT center and stem cells (for at least 2 transplants) should be harvested.



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Stem Cell Transplants

High-dose therapy with stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with MM. The types of SCT may be single autologous SCT, a tandem SCT (a planned second course of high-dose therapy and SCT within 6 months of the first course), or an allogeneic SCT. An allogeneic SCT can be performed after prior myeloablative therapy or after nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as “mini transplant,” has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.^{130,131} It is important to note that nonmyeloablative allogeneic transplant by itself is not adequate therapy and is usually done following maximal tumor control through adequate induction therapy or an autologous SCT. An allogeneic SCT may also follow an autologous SCT.

The NCCN Guidelines for Multiple Myeloma indicate that all types of SCT are appropriate in different clinical settings; these indications are discussed further below. In general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. However, renal dysfunction is not an absolute contraindication to transplant. Earlier studies of autologous transplant included total body irradiation (TBI) as a component of the preparative regimen. Regimens with chemotherapy have been shown to have equivalent efficacy and less toxicity than TBI. TBI regimens have now been abandoned,¹³² but newer, potentially less toxic radiation techniques aimed to deliver total marrow irradiation while reducing toxicities to non-target organs are currently undergoing evaluation in clinical trials.¹³³

Autologous Stem Cell Transplants

Autologous SCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significantly higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy.¹³⁴ In 2003, results of a second trial comparing high-dose therapy to standard therapy showed an increase in the CR rate and an improvement in OS (54 months in the high-dose group compared to 42 months for standard therapy).¹³⁵ Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous stem cell support or standard therapy.¹³⁶ With a median follow-up of 76 months, there were no differences in response rates, PFS, or OS between the two groups. The reason for the discrepant results are not clear, but may be related to differences in the specific high-dose and conventional regimens between the American and French study. For example, the American study included TBI as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.¹³²

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.¹³⁷ This study was specifically designed to include older patients, since the median age of the participants in other trials ranged from 54 to 57 years and the median age in this trial was 61 years. After 120 months of follow-up, there was no significant difference in OS, although there was a trend toward improved EFS in the high-dose group ($P = .7$). Additionally, the period of time without symptoms, treatment, or treatment toxicity (TWiSTT) was significantly longer in the high-dose group. The study concluded that the equivalent survival suggests that the treatment choice between high-dose and

conventional-dose chemotherapy should be based on personal choice in older patients. For example, an early transplant may be favored because patients can enjoy a longer interval of symptom-free time. However, this study¹³⁸ also showed that a transplant performed at relapse has a similar OS compared to an early transplant. The choice of early versus late transplant was examined in a randomized French trial, and the results in both arms are comparable with respect to OS.¹³⁹ However, early SCT was superior in terms of quality of life, assessed as time without symptoms and side effects from therapy.¹³⁹ However, these early randomized studies of autologous SCT after primary therapy were designed and implemented before the availability of newer drugs.

A recent phase III study compared high-dose melphalan followed by autologous SCT with MPR (melphalan, prednisone, and lenalidomide). Patients (n = 402) were randomly assigned (in a 1:1:1:1 ratio) to one of the four groups: high-dose therapy and autologous SCT followed by maintenance with lenalidomide; high-dose therapy and SCT alone; primary therapy with MPR followed by lenalidomide; and primary therapy with lenalidomide alone. The primary study endpoint was PFS. Secondary endpoints included OS, the ORR, the time to a response, and safety.¹⁴⁰ The comparison of the group treated with high-dose melphalan therapy followed by autologous SCT with MPR shows that high-dose melphalan therapy followed by autologous SCT was associated with a significant reduction in the risk of progression or death (HR, 0.44) and prolonged OS (HR for death, 0.55).¹⁴⁰

Results from the IFM 2005/01 study of patients with symptomatic myeloma receiving primary therapy with bortezomib and dexamethasone versus VAD showed a marked improvement in ORR with bortezomib and dexamethasone over VAD (see *Preferred Primary Therapy Regimens for Transplant Candidates*).⁹⁸ Responses were evaluated after primary treatment and post-autologous SCT. After the

first autologous SCT, CR/near-CR rates were 35.0% in the bortezomib plus dexamethasone arm, compared with 18.4% in the VAD arm.⁹⁸ The VGPR rates were 54.3% versus 37.2%. Median PFS was 36.0 months versus 29.7 months ($P = .064$) with bortezomib plus dexamethasone versus VAD after a median follow-up of 32.2 months.⁹⁸ Also, PFS was also significantly longer in the patients achieving greater than or equal to a VGPR after primary treatment than in patients achieving a less than VGPR (median 36 vs. 29.7 months).⁹⁸

In another study, 474 patients were randomized to primary therapy with bortezomib/dexamethasone/thalidomide (n = 236) or thalidomide/dexamethasone (n = 238) before double autologous SCT.¹⁴¹ The 3-drug regimen yielded high response rates compared with the 2-drug regimen, with a CR rate of 19% (vs. 5%) and greater than or equal to VGPR of 62% (vs. 31%). After SCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone.

The IFM 2009 phase III trial compared the efficacy and safety of bortezomib/lenalidomide/dexamethasone alone versus bortezomib/lenalidomide/dexamethasone plus autologous SCT for the treatment of newly diagnosed MM in patients 65 years or younger.¹⁴² The reported CR rate was 48% in the group that received induction therapy alone versus 59% in the transplantation group ($P = .03$). No MRD was detected in 65% of the patients who received bortezomib/lenalidomide/dexamethasone alone versus no MRD in 79% of the patients who received induction therapy plus autologous SCT ($P < .001$).¹⁴² There was a clear improvement in PFS with SCT (50 months vs. 36 months). These results clearly show the benefit of autologous SCT, with higher rates of durable responses in those with no MRD after initial therapy.¹⁴² Taken together, the studies suggest that improved responses with the primary regimen result in improved outcomes after



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transplantation even for patients receiving an IMiD and PI-based triplet regimen.

The OS of patients in the IFM 2009 phase III trial was high in both groups—the one that received autologous SCT and the one that did not.¹⁴² Although autologous SCT improved PFS it did not improve OS, suggesting that delaying SCT is an option and is not associated with negative effects on OS.

According to the NCCN Guidelines, for transplant-eligible patients autologous SCT is an option after primary induction therapy (category 1) and for treatment of progressive/refractory disease after primary treatment.

Tandem Stem Cell Transplants

Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first course. Planned tandem transplants have been studied in several randomized trials. The IFM94 trial reported by Attal et al randomized newly diagnosed patients with MM to single or tandem autologous transplants.¹⁴³ A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months after the first. A variety of options for therapy of relapsed disease were provided. For example, relapsing patients in either group underwent either no therapy, additional conventional therapy, or another SCT. The probability of EFS for 7 years after the diagnosis was 10% in the single transplant group compared to 20% in the double transplant group. In a subset analysis, those patients who did not achieve a complete CR or a VGPR within 3 months after the first transplant appeared to benefit the most from a second transplant. The investigators of the IFM94 study have suggested that the improvement in projected survival associated with tandem transplant is related not to improved response rates, but to

longer durations of response. Four other randomized trials have compared single versus tandem transplant.^{137,144-146} None of these trials showed a significant improvement in OS. However, since the median follow-up in these trials ranged from 42 to 53 months, the lack of significant improvement is not surprising. The trial by Cavo et al¹⁴⁴ found that patients not in CR or near-CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non-TBI-based high-dose regimens.

In both the French and Italian trials, the benefit of a second autologous SCT was seen in patients who do not achieve a CR or VGPR (greater than 90% reduction in M-protein level) with the first procedure. These two studies were not adequately powered to evaluate the equivalence of one versus two transplants in patients achieving a CR or VGPR after the first transplantation.

A review of long-term outcomes of several trials of autologous transplantation by Barlogie et al found that tandem transplantations were superior to both single transplantations and standard therapies.¹⁴⁷ Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.¹⁴⁷ The NCCN Multiple Myeloma Panel recommends collecting enough stem cells for 2 transplants in *all* eligible patients. According to the NCCN Multiple Myeloma Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al¹⁴⁰ (discussed in the previous section, page MS-22), which addressed the role of maintenance therapy with lenalidomide after autologous transplantation.¹⁴⁰ Although associated with more frequent grade 3 or 4

neutropenia and infections, maintenance therapy with lenalidomide was found to significantly reduce risk of disease progression or death (HR, 0.47) after both single and tandem transplantation compared with no maintenance.¹⁴⁰

The recently reported results of a phase III trial (StaMINA) indicate that a tandem autologous SCT followed by lenalidomide maintenance has similar outcomes to a single autologous SCT followed by lenalidomide maintenance in the initial treatment of MM.¹⁴⁸ Another recently reported result of an intergroup, multicenter, phase III study (EMN02/HO95 MM Trial) suggests that tandem autologous SCT for newly diagnosed MM appears to be superior in extending PFS compared with single autologous SCT after induction therapy with a bortezomib-based regimen.¹⁴⁹

A second autologous SCT can be considered at the time of disease relapse. A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous SCT to those treated with conventional chemotherapy for relapsed MM.¹⁵⁰ Similar to previously published smaller studies,¹⁵¹⁻¹⁵³ this retrospective analysis demonstrated that a second autologous SCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs. 78%), along with improved OS (32% vs. 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (<55 years), beta-2 microglobulin <2.5 mg/L at diagnosis, a remission duration of >9 months, and a greater than PR to their first autologous SCT. This analysis indicates that a second autologous transplant, for relapsed or progressive MM, may be an option for carefully selected patients. Some of these patients can achieve durable complete or partial remission.^{153,154}

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus second autologous SCT with cyclophosphamide in patients with relapsed MM who had received autologous SCT as primary treatment.¹⁵⁵ The patients included in the study were greater than 18 years of age and needed treatment for progressive or relapsed disease at least 18 months after a previous autologous SCT. All patients first received bortezomib/doxorubicin/dexamethasone induction therapy. Patients with adequately harvested stem cells then were randomized to high-dose melphalan plus second autologous SCT (n = 89) or oral cyclophosphamide (n = 85). The primary endpoint was time to disease progression.¹⁵⁵ After a median follow-up of 31 months, median time to progression in patients who underwent second autologous SCT after induction therapy was 19 months versus 11 months for those treated with cyclophosphamide (HR, 0.36 [95% CI, 0.25–0.53]; $P < .0001$). Grade 3–4 neutropenia (76% vs. 13%) and thrombocytopenia (51% vs. 5%) were higher in the group that underwent autologous SCT versus cyclophosphamide.¹⁵⁵ Median OS in the SCT group was 67 months versus 52 months in the cyclophosphamide maintenance group.¹⁵⁶

According to the NCCN Multiple Myeloma Panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding SCT and documented progression. Data from retrospective studies¹⁵⁷⁻¹⁶⁰ suggest 2 to 3 years as the minimum length of remission for consideration of second autologous SCT for relapsed disease.

Allogeneic Stem Cell Transplant

Allogeneic SCT includes either myeloablative or nonmyeloablative (ie, “mini” transplant) transplants. Allogeneic SCT has been investigated as an alternative to autologous SCT to avoid the contamination of



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re-infused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Non-myeloablative transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between myeloablative and nonmyeloablative transplants relates to the chemotherapy regimen used. Specific preparatory regimens have not been a focus of the NCCN Guidelines, and therefore these guidelines do not make a distinction between these approaches.

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic to autologous SCT, but multiple case series have been published describing allogeneic SCT as an initial therapy or as therapy for relapsed/refractory MM. In a 1999 review, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.¹⁶¹ Other reviews have also reported increased morbidity without convincing proof of improved survival.^{162,163} However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.¹³⁶ The original trial had an ablative, allogeneic transplant group consisting of patients with HLA identical siblings. Thirty-six patients received allografts, and due to the high 6-month mortality of 45%, the allogeneic arm was closed. After 7 years of follow-up the OS of the conventional chemotherapy, autologous, and allogeneic arms were all identical at 39%. The autologous and conventional chemotherapy arms do not demonstrate a plateau, whereas the allogeneic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in

myeloablative allogeneic SCT, particularly given the lack of a significant cure rate for single or tandem autologous SCT.

The NCCN Guidelines consider myeloablative allogeneic SCT an accepted option, preferably in a clinical trial in: 1) patients whose disease responds to primary therapy; 2) patients with primary PD; or 3) patients with PD after an initial autologous SCT.

Another strategy that has been investigated is initial autologous SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al¹⁶⁴ showed that, among patients (<65 years) with HLA-matched siblings who received an autograft-allograft regimen, CR rate after allografting was 55%, compared with 26% after double autograft in patients without HLA-matched siblings. Median OS was higher (80 vs. 54 months). In the prospective PETHEMA trial in patients who did not achieve at least near-CR with a first autologous SCT, there was no significant difference in OS after double autologous SCT versus autologous SCT followed by mini-allogeneic transplant. However, a trend toward a longer PFS was observed in the group treated with autologous SCT followed by mini-allogeneic transplant.¹⁶⁵ In contrast, the IFM trial (99-03) by Garban et al¹⁶⁶ and the BMT-CTN 0102 trial¹⁶⁷ reported no OS or PFS advantage with autologous transplant followed by allogeneic transplant in any subgroup, even after 10 years of follow-up.

In a prospective study of patients with previously untreated MM, patients were selected for treatment with autologous SCT followed by reduced-intensity conditioning allogeneic SCT or autologous SCT based on the availability of an HLA-identical sibling.¹⁶⁸ The induction chemotherapy in this study consisted of the chemotherapy that was standard at the time — the VAD or VAD-like regimen. After 60 months, the incidence of relapse/disease progression was 49% in the group



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treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT versus 78% in the autologous SCT group. At 60 months, the OS and CR rates were 65% and 51%, respectively, for patients treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT compared with 58% and 41% for those treated with autologous SCT. Based on these study results, patients who have an HLA-identical sibling may be considered candidates for reduced-intensity allogeneic SCT as part of their first-line treatment.

Mini-allogeneic transplants have also been investigated as therapy for relapsed/refractory disease by virtue of their graft-versus-myeloma effect. Responsive disease to prior transplantation and younger age are associated with better response and OS rates.¹⁶⁹⁻¹⁷² In a case series report, 54 patients with previously treated relapsed disease or PD were treated with an autologous SCT followed by a mini-allogeneic transplant.¹⁷⁰ There was a 78% OS at a median 552 days after the mini-allogeneic transplant, with a 57% CR rate and an ORR of 83%. This study concluded that this approach reduced the acute toxicities of a myeloablative allogeneic SCT while preserving anti-tumor activity. The largest case series was reported by the EBMT.¹⁷¹ In this heterogeneous population of 229 patients, the 3-year OS and PFS were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease and more than 1 prior transplant, whereas improved¹⁷³ OS was associated with graft-versus-host disease (GVHD), confirming the importance of a graft-versus-leukemia effect. This study concluded that mini-allogeneic transplantation is feasible, but heavily pretreated disease and patients with PD are unlikely to benefit.

Patients whose disease either does not respond to or relapses after allogeneic stem cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect¹⁷⁴⁻¹⁸¹ or other myeloma therapies on or off a clinical trial.

Follow-Up After Stem Cell Transplantation

Follow-up tests after SCT are similar to those done after primary myeloma therapy (see page MS-20).

In addition, MRD assessment is increasingly being incorporated into post-treatment assessments. MRD has been identified as an important prognostic factor. A prospective study of patients with newly diagnosed MM evaluated MRD in bone marrow samples and showed that at a median follow-up of 57 months, MRD negativity after autologous SCT translated to significantly improved PFS and OS rates.¹⁸² Similarly, in another study, MRD negativity after autologous SCT was predictive of favorable PFS and OS.¹⁸³

Similar results have also been reported in the allogeneic SCT setting where the presence of MRD after allogeneic SCT has been associated with a significantly adverse PFS and OS.¹⁷³ The NCCN panel recommends assessing for MRD during follow-up as indicated.⁴⁴

Maintenance Therapy

Lenalidomide as Maintenance Therapy After Autologous SCT

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies.^{120,121}

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n = 231) versus placebo (n = 229) after autologous SCT.¹²¹ At a median follow-up of 34 months, 37% of the patients who received lenalidomide versus 58% who received placebo had disease progression or died. The median time to progression in the lenalidomide group was 46 months versus 27 months in the placebo group ($P < .001$). Second primary cancers occurred in 18 patients who



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received lenalidomide (8%) and in 6 patients who received placebo (3%).¹²¹

Data from the international, randomized, double-blind phase III IFM 2005-02 trial (n = 614) show that patients treated with lenalidomide as consolidation therapy after an autologous SCT followed by lenalidomide as maintenance therapy had upgraded responses. Of the 614 patients enrolled in the trial, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Maintenance treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. The final analysis of the IFM 2005-02 trial was performed after a median follow-up of 30 months and 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median PFS was 41 months in the lenalidomide group, compared with 23 months in the placebo group (HR, 0.50; $P < .001$; median follow-up period was 30 months). The probability of surviving without progression for 3 years after randomization was 59% in those treated with lenalidomide and 35% in those who received the placebo. The benefit of lenalidomide maintenance therapy, evidenced by rate of PFS at 3 years after randomization, was higher in all patients who received lenalidomide maintenance therapy compared with those who received placebo. This benefit was observed in patients who had a VGPR at randomization (64% vs. 49%, $P = .006$) and those who did not (51% vs. 18%, $P < .001$).¹²⁰ An increased incidence of second primary cancers was observed in the lenalidomide group (32 had second primary cancers in the lenalidomide group and 12 in the placebo group).¹²⁰ The updated survival analysis of the same study after 91 months for follow-up reported median time to progression of 57.3 months (95% CI, 44.2–73.3) with lenalidomide and 28.9 months (23.0–36.3) with placebo (HR, 0.57; 95% CI, 0.46–0.71; $P < .0001$).¹⁸⁴ The most common grade 3-4

adverse events in the lenalidomide group compared to placebo were neutropenia (50% vs. 18%) and thrombocytopenia (15% vs. 5%). An increased rate of second primary malignancies (hematologic plus solid tumor) were diagnosed in the lenalidomide group compared with placebo (14% vs. 4%).¹⁸⁴

The study by Palumbo et al¹⁴⁰ (discussed in *Autologous Stem Cell Transplants*) showed that although maintenance therapy with lenalidomide is associated with more frequent grade 3 or 4 neutropenia and infections, it significantly reduced risk of disease progression or death (HR, 0.47) compared with no maintenance.¹⁴⁰

The benefit of lenalidomide maintenance was studied in a meta-analysis of data from 1209 patients enrolled in the trials discussed above randomized to maintenance with lenalidomide or placebo.¹⁸⁵ The study showed improved median PFS with lenalidomide maintenance (52.8 vs. 23.5 months; HR 0.48; 95% CI, 0.42–0.55). At 7 years, the OS was 62% in the group receiving lenalidomide maintenance versus 50% in those receiving placebo. In those with high-risk cytogenetics, a PFS benefit, but not an OS benefit was seen with lenalidomide maintenance versus placebo.

The lenalidomide group had higher rates of second primary malignancy occurring before progression, and the rates of PD were higher in the group receiving placebo.

Maintenance therapy after allogeneic transplant: A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic SCT.¹⁸⁶ However, another recently reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic SCT in patients with high-risk MM.¹⁸⁷

Lenalidomide as Maintenance Therapy After Non-Transplant Primary Treatment

Data from the phase III MM-015 study show that lenalidomide maintenance after primary therapy with melphalan/prednisone/lenalidomide (MPL) significantly reduced the risk of disease progression and also increased PFS.¹⁸⁸ In this study, newly diagnosed patients with MM (n = 459) aged ≥ 65 years were randomized to receive MP followed by placebo, MPL, or MPL followed by lenalidomide until progression. Maintenance with lenalidomide significantly prolonged PFS. The PFS of patients treated with MPL followed by maintenance lenalidomide was significantly prolonged (n = 152; median, 31 months) compared with the other two arms: MPL (n = 153; median, 14 months; HR, 0.49; $P < .001$) or MP (n = 154; median, 13 months; HR, 0.40; $P < .001$). Lenalidomide maintenance therapy improved PFS by 66% compared with placebo, regardless of age.¹⁸⁸ In the FIRST trial, use of lenalidomide indefinitely until progression was associated with a superior PFS compared with a fixed duration of 18 months.

Based on the evidence from the phase III trials,^{120,121,188} the NCCN Multiple Myeloma Panel lists single-agent lenalidomide as one of the preferred maintenance regimens (category 1). Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially post-transplantation,^{120,121,189} or after a melphalan-containing regimen.¹²³ According to the results of the FIRST trial, in the continuous lenalidomide/dexamethasone arm, the absence of the alkylator melphalan seems to be more effective in terms of improving PFS and lowering incidence of second malignancies.¹¹⁹

A meta-analysis of 4 randomized controlled trials examined patients treated with lenalidomide maintenance versus patients with no

maintenance or placebo in both the transplant and non-transplant settings.¹⁹⁰ The analysis showed that patients treated with lenalidomide maintenance had significantly improved PFS (HR, 0.49; $P < .001$) and a trend toward OS (HR, 0.77; $P = .071$) versus no maintenance or placebo.¹⁹⁰ There was significantly more grade 3/4 neutropenia with the use of lenalidomide and a 2-fold increased risk of secondary malignancies.

The benefits of improved PFS with lenalidomide maintenance must be weighed against the increased rate of severe (grade 3 and 4) neutropenia, risk of second cancers, and other toxicities.¹⁹¹ The NCCN panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Other Recommended Maintenance Regimens

Bortezomib as Maintenance Therapy After Autologous SCT

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR.⁸⁶ Patients in the HOVON trial were randomly assigned to one of the two arms consisting of either primary treatment with vincristine/doxorubicin/dexamethasone followed by autologous SCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed by autologous SCT and bortezomib as maintenance therapy for 2 years. The study reported high near-CR/CR rates after primary treatment with the bortezomib-based regimen. Bortezomib as maintenance therapy was well tolerated and associated with additional improvement of response rates⁸⁶ (see *Preferred Primary Therapy Regimens for Transplant Candidates*).



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A multicenter phase III trial in newly diagnosed patients with MM showed that consolidation with bortezomib after autologous SCT improved PFS only in patients not achieving at least VGPR after autologous SCT.¹⁹² There was no difference in PFS in patients with $\geq$ VGPR after autologous SCT.

Bortezomib as Maintenance Therapy After Non-Transplant Active Primary Treatment

The preliminary results of the phase III UPFRONT study also show that maintenance with single-agent bortezomib is well-tolerated when administered after treatment with bortezomib-based primary therapy.¹⁹³ Newly diagnosed patients with MM ineligible for high-dose therapy and SCT enrolled in the UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib and dexamethasone; bortezomib in combination with thalidomide and dexamethasone; or bortezomib with melphalan and prednisone followed by maintenance treatment with bortezomib. The updated results show that the response rates, including CR and $\geq$ VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of peripheral neuropathy.¹⁹³

The NCCN Multiple Myeloma Panel Members have added bortezomib as a maintenance therapy option.

Treatment of Progressive or Relapsed Myeloma

Therapy for previously treated relapsed/refractory MM is considered in the following clinical situations: patients with relapsed disease after allogeneic or autologous SCT; patients with primary PD after initial autologous or allogeneic SCT; and patients ineligible for SCT with progressive or relapsing disease after initial primary therapy.

A variety of therapies are available as options for previously treated MM depending on the prior therapy and duration of response. The options include systemic therapy; SCT (for eligible patients who did not receive SCT as part of their initial treatment); or clinical trial. For those who had autologous SCT as part of initial treatment and had a durable response or had SD, consideration must be given to a second transplantation on or off clinical trial at the time of relapse/disease progression.

If the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.

Preferred Regimens for Previously Treated Multiple Myeloma

Bortezomib/Lenalidomide/Dexamethasone

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase I and phase II studies show that bortezomib/lenalidomide/dexamethasone is well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide, bortezomib, thalidomide, and SCT.^{194,195}

The updated data after over 2 years of follow-up report a median PFS of 9.5 months and median OS of 26 months, with 12- and 24-month OS rates of 86% and 55%, respectively.¹⁹⁶ The NCCN Multiple Myeloma Panel Members have included bortezomib/lenalidomide/dexamethasone as a preferred option for relapsed/refractory MM.

Carfilzomib/Lenalidomide/Dexamethasone

A randomized, multicenter phase III trial of 792 patients (ASPIRE) studied the combination of lenalidomide and dexamethasone with or without carfilzomib in patients with relapsed/refractory myeloma who



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had received one to three prior lines of therapy. The primary endpoint of the study was PFS. The results showed that addition of carfilzomib to lenalidomide and dexamethasone significantly improved PFS by 8.7 months (26.3 months for the carfilzomib arm vs. 17.6 months for lenalidomide and low-dose dexamethasone; HR for progression or death, 0.69; 95% CI, 0.57–0.83; $P = .0001$). The median duration of treatment was longer in the carfilzomib group (88.0 weeks vs. 57 weeks). The incidence of peripheral neuropathy was nearly identical in both arms (17.1% in the carfilzomib group vs. 17.0%). Non-hematologic adverse effects ($\geq$ grade 3) that were higher in the carfilzomib group compared with lenalidomide and dexamethasone included dyspnea (2.8% vs. 1.8%), cardiac failure (3.8% vs. 1.8%), and hypertension (4.3% and 1.8%). There were fewer discontinuations due to side effects in the carfilzomib arm (15.3% vs. 17.7%). Patients in the carfilzomib arm reported superior health-related quality of life than those who received lenalidomide and dexamethasone.¹⁹⁷

Based on the above data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib with lenalidomide and dexamethasone as a preferred option for patients with relapsed/refractory myeloma (category 1).

Carfilzomib (twice weekly)/Dexamethasone

The results of the phase III ENDEAVOR trial in patients with relapsed/refractory MM treated with multiple prior lines of therapy showed a 2-fold improvement in median PFS with carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; HR = 0.53; $P < .0001$).¹⁹⁸ ORR was 77% in the carfilzomib group versus 63% in the bortezomib group; rates of CR or better were 13% and 6% and rates of VGPR were 42% and 22%, respectively. Median duration of response was 21.3 months in the

carfilzomib group and 10.4 months in the bortezomib group. Adverse events (grade 3 or higher) in the carfilzomib arm compared to the bortezomib arm included hypertension (6% vs. 3%), anemia (12% vs. 9%), thrombocytopenia (10% vs. 14%), and dyspnea (5% vs. 2%). Rate of grade ≥ 2 peripheral neuropathy was 6% in the carfilzomib group and 32% in the bortezomib group.¹⁹⁸

The OS analysis showed that those treated with carfilzomib/dexamethasone lived 7.6 months longer (median OS was 47.6 months in the carfilzomib group vs. 40 months in the bortezomib group; HR, 0.791 [95% CI, 0.648–0.964]; $P = .010$).¹⁹⁹ The most frequent grade 3 or worse adverse events in the carfilzomib arm compared to the bortezomib arm included hypertension (15% vs. 3%), anemia (16% vs. 10%), dyspnea (6% vs. 2%), decreased lymphocyte count (6% vs. 2%), diarrhea (4% vs. 9%), and peripheral neuropathy (1% vs. 6%).¹⁹⁹ Rates of thrombocytopenia, pneumonia, and fatigue were similar in both groups.¹⁹⁹

Based on the above phase III data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib (twice weekly) and dexamethasone as a preferred option for patients with relapsed/refractory myeloma (category 1).

Daratumumab/Bortezomib/Dexamethasone

A phase III trial showed that adding daratumumab to bortezomib and dexamethasone markedly improved outcomes for patients with recurrent/refractory MM. Patients ($n = 498$) were randomized to receive daratumumab/bortezomib/dexamethasone or bortezomib/dexamethasone. The ORR in the daratumumab arm was 82.9% compared to 63.2% in the control arm ($P < .001$). The rates of VGPR and CR were double in the daratumumab arm compared to the control arm (59.2% vs. 29.1%, $P < .001$ and 19.2% vs. 9.0%, $P = .001$,

respectively). The 12-month estimated rate of PFS was significantly higher in the daratumumab arm compared to the control (60.7% vs. 26.9%). The most common grade 3 or 4 adverse events reported in daratumumab and control groups were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively). Grade 1 or 2 infusion-related reactions associated with daratumumab were reported in 45.3% of the patients in the daratumumab group and grade 3 in 8.6% of the patients. These infusion-related reaction rates are consistent with findings from previous trials of daratumumab.^{200,201}

Based on the above phase III data, the NCCN panel has added daratumumab/bortezomib/dexamethasone as a preferred option (category 1) for the treatment of patients with relapsed/refractory MM.

Daratumumab/Lenalidomide/Dexamethasone

A phase III trial randomized patients (n = 569) 1:1 to receive daratumumab/lenalidomide/dexamethasone or lenalidomide/dexamethasone.²⁰²

According to the reported results, the ORR (in patients with an evaluable response) was higher in the daratumumab group (92.9% vs. 76.4%; $P < .001$) and so was the CR (43.1% vs. 19.2%, $P < .001$). In the group that received daratumumab, the estimated rate of PFS at 12 months was 83.2% (95% CI, 78.3–87.2) compared with 60.1% (95% CI, 54.0–65.7) in the lenalidomide/dexamethasone group. Since deeper responses are known to result in longer PFS, a subgroup analysis showed that in those having a PR or better, the rate of PFS at 12 months was 87.8% (95% CI, 83.1–91.3) with daratumumab versus 73.6% (95% CI, 67.0–79.1) with lenalidomide/dexamethasone. Among patients with a VGPR or better, the rate of PFS was further improved: 91.7% (95% CI, 87.1–94.8) in the daratumumab group versus 85.8%

(95% CI, 78.1–90.9) in the lenalidomide/dexamethasone group. The estimated rate of OS at 12 months in the daratumumab group was also significantly higher: 92.1% (95% CI, 88.2–94.7) compared with 86.8% (95% CI, 82.2–90.3) in the lenalidomide/dexamethasone group.

The most common adverse events of grade 3 or 4 in patients treated with the daratumumab regimen versus lenalidomide/dexamethasone were neutropenia (51.9 vs. 37.0%), thrombocytopenia (12.7% vs. 13.5%), and anemia (12.4% vs. 19.6%). Daratumumab-associated infusion-related reactions (mostly grade 1 or 2) were reported in 47.7% of the patients.

Based on the above phase III data, the NCCN panel has added daratumumab/lenalidomide/dexamethasone as a preferred option (category 1) for the treatment of patients with relapsed/refractory MM.

Elotuzumab/Lenalidomide/Dexamethasone

Elotuzumab is a humanized monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7). SLAMF7, also called CS1 (cell-surface glycoprotein CD2 subset 1) is a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues.²⁰³ The FDA has approved elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies. This is based on the results of the phase III trial, ELOQUENT-2. The trial randomized 646 patients (1:1) to receive either elotuzumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone.²⁰⁴

The rates of PFS at the end of 1 and 2 years were higher for those receiving the elotuzumab-containing regimen (68% at 1 year and 41% at 2 years) compared with those receiving lenalidomide and



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dexamethasone alone (57% at 1 year and 27% at 2 years).²⁰⁴ Median PFS in the group receiving the elotuzumab-containing regimen was 19.4 months versus 14.9 months in those receiving lenalidomide and dexamethasone alone (HR for progression or death in the elotuzumab group, 0.70; 95% CI, 0.57–0.85; $P < .001$) indicating a relative reduction of 30% in the risk of disease progression or death.²⁰⁴ Common grade 3 or 4 adverse events in both arms of the trial were lymphocytopenia, neutropenia, fatigue, and pneumonia. Infusion reactions occurred in 33 patients (10%) in the elotuzumab group and were grade 1 or 2 in 29 patients.²⁰⁴

Consistent with the above finding, in a subset analyses of extended 3-year follow-up, median duration of response reported with the 3-drug combination was 20.3 months versus 16.6 months with lenalidomide and dexamethasone showing that PFS benefit with the triple regimen was durable over time.²⁰⁵

Based on the above data and FDA approval the NCCN panel has included elotuzumab in combination with lenalidomide and dexamethasone as a preferred regimen option (category 1) for previously treated MM.

Ixazomib/Lenalidomide/Dexamethasone

A double-blind, randomized, placebo-controlled phase III TOURMALINE MM1 trial randomized 722 patients with relapsed and/or refractory MM to a combination of ixazomib plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone (control group). This trial was designed based on the promising results of a phase I/II study (discussed under *Other Recommended Primary Therapy Regimens for Transplant Candidates*).⁹⁶

The results of the TOURMALINE MM1 trial show a significant improvement in PFS with the ixazomib-containing regimen. After a median follow-up of almost 15 months, a 35% improvement in PFS was seen in the group treated with the ixazomib regimen compared with the control group (HR, 0.74; $P = .01$). Median PFS was 20.6 months in the ixazomib-treated group versus 14.7 months in the group receiving lenalidomide and dexamethasone alone. In the ixazomib-treated group versus the control group, the ORR (78% vs. 72%, $P = .035$) and CR (11.7% vs. 6.6%, $P = .019$) were also improved. Of note, patients with high-risk cytogenetics enrolled in the trial receiving ixazomib had a similar HR for PFS as the entire study population (HR, 0.596 and 0.543, respectively). Grade ≥ 3 adverse events were reported in 74% and 69% of patients in the ixazomib-treated and control groups, respectively. These included anemia (9% with ixazomib/lenalidomide/dexamethasone vs. 13% with lenalidomide/dexamethasone), thrombocytopenia (19% vs. 9%), and neutropenia (23% vs. 24%). The addition of the ixazomib/lenalidomide/dexamethasone group had a slightly higher rate of peripheral neuropathy compared to lenalidomide/dexamethasone (27% vs. 22%).

Based on the results of the phase III TOURMALINE MM1 trial,²⁰⁶ the NCCN panel has included ixazomib/lenalidomide/dexamethasone as a preferred regimen option for previously treated MM.

Other Recommended Regimens for Previously Treated MM

Bendamustine/Lenalidomide/Dexamethasone

A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients ($n = 29$) with relapsed/refractory MM.²⁰⁷ PR rate was seen in 52% ($n = 13$) of patients, with VGPR in 24% ($n = 6$) of patients. The



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median PFS in the trial was 6.1 months (95% CI, 3.7–9.4 months), and the one-year PFS rate was 20% (95% CI, 6%–41%).²⁰⁷ The NCCN panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.

Bendamustine/Bortezomib/Dexamethasone

A phase II study evaluated bendamustine/bortezomib/dexamethasone administered over six 28-day cycles and then every 56 days for six more cycles in patients (n = 75; median age 68 years) with relapsed/refractory MM treated with multiple prior therapies and *not* refractory to bortezomib. The PR rate was 71.5% (16% CR, 18.5% VGPR, 37% partial remission). At 12-month follow-up, median time to progression was 16.5 months and 1-year OS was 78%.²⁰⁸

Bortezomib/Liposomal Doxorubicin/Dexamethasone

Bortezomib with liposomal doxorubicin (PLD) was approved by the FDA as a treatment option for patients with MM who have not previously received bortezomib and have received at least one prior therapy. The approval was based on a priority review of data from an international phase III trial (n = 646) showing that use of the combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).²⁰⁹ Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. Based on these results, the NCCN Multiple Myeloma Panel considers bortezomib with the PLD regimen as a category 1 option for patients with relapsed/refractory MM.

Bortezomib/Cyclophosphamide/Dexamethasone

The effects of adding of an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory MM. The combination of bortezomib,

dexamethasone, and cyclophosphamide was found to be effective in patients with relapsed/refractory myeloma with an acceptable toxicity profile.^{210,211} The NCCN Multiple Myeloma Panel members have included bortezomib/cyclophosphamide/dexamethasone to the list of options for relapsed/refractory MM.

Bortezomib/Dexamethasone

Addition of dexamethasone to bortezomib in patients with relapsed/refractory myeloma who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.²¹²⁻²¹⁴ The NCCN Multiple Myeloma Panel members have included the bortezomib and dexamethasone regimen as an option for patients with relapsed/refractory myeloma (category 1).

Carfilzomib (weekly)/Dexamethasone

The data from a phase 1 study (CHAMPION-1) determined the maximum tolerated dose of carfilzomib (in combination with dexamethasone) to be 70 mg/m², once weekly.²¹⁵ Subsequently, a phase II study was conducted in patients with relapsed/refractory MM (n = 104) to evaluate safety and efficacy of weekly dosing of carfilzomib with dexamethasone. The ORR observed in this study was 77% (95% CI, 68–85). At 13.6 months, the median PFS was 16.2 months (95% CI, 10.2–21.0).²¹⁶ The most common grade 3 or higher adverse events occurring in at least 3% of all patients were fatigue (11%), pneumonia (6%), acute kidney injury (7%), and hypertension (8%).

The NCCN Multiple Myeloma Panel has included the carfilzomib (weekly)/dexamethasone regimen as an option for patients with relapsed/refractory myeloma.



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Carfilzomib/Cyclophosphamide/Dexamethasone

A phase II trial compared the safety and toxicity of carfilzomib/cyclophosphamide/dexamethasone with bortezomib/cyclophosphamide/dexamethasone in patients who had received one prior regimen for relapsed/refractory MM. The study reported carfilzomib/cyclophosphamide/dexamethasone as well tolerated with toxicity profile of carfilzomib being similar to that seen in other trials. This regimen is included in the NCCN Guidelines for Multiple Myeloma as an option for patients with relapsed/refractory myeloma.

Lenalidomide/Dexamethasone

Lenalidomide combined with dexamethasone received approval from the FDA as a treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of a total of 692 patients randomized to receive dexamethasone either with or without lenalidomide. The primary efficacy endpoint in both studies was time to progression. A pre-planned interim analysis of both studies reported that the median time to progression was significantly longer in the lenalidomide arm compared to the control group.^{217,218} The updated clinical data from the pivotal North American phase III trial (MM-009) in 353 previously treated patients with MM reported increased OS and median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo.²¹⁸ Similar results were seen in the international trial MM-010.²¹⁷ Patients in both of these trials had been heavily treated before enrollment. Many had 3 or more prior lines of therapies with other agents and more than 50% of patients having undergone SCT.^{217,218} Most adverse events and grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide/dexamethasone compared to placebo and

dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The NCCN Multiple Myeloma Panel now considers this regimen as a category 1 option as therapy for patients with relapsed/refractory MM. Lenalidomide monotherapy has also been investigated and found effective in patients with relapsed/refractory MM.²¹⁹ The NCCN Multiple Myeloma Panel suggests considering lenalidomide monotherapy for steroid-intolerant individuals.

Lenalidomide/Cyclophosphamide/Dexamethasone

A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.²²⁰

Pomalidomide/Dexamethasone

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.²²¹ The results of a phase I study of pomalidomide (4 mg orally on days 1–21 of each 28-day cycle), with or without dexamethasone (40 mg/wk), showed encouraging activity with manageable toxicity in patients with relapsed/refractory MM, including those refractory to both lenalidomide and bortezomib.²²² A subsequent phase II randomized, open-label study evaluated the combination of pomalidomide and low-dose dexamethasone versus single-agent pomalidomide in patients with relapsed, refractory MM who had received a trial of lenalidomide and bortezomib.²²³ Of the 221 patients who were evaluated after a median follow-up of 14.2 months, the median PFS was 4.2 months in patients treated with pomalidomide plus low-dose dexamethasone compared with 2.7 months in patients treated with pomalidomide (HR, 0.68; $P = .003$).²²⁴ The median OS was 16.5 months compared to 13.6 months with pomalidomide alone.²²⁴ Grade 3

to 4 neutropenia occurred in 41% of patients treated with pomalidomide plus low-dose dexamethasone versus 48% of patients treated with pomalidomide monotherapy. No grade 3 to 4 peripheral neuropathy was reported.

A phase III, multicenter, randomized, open-label study (MM-003) conducted in Europe compared the efficacy and safety of pomalidomide and low-dose dexamethasone (n = 302) versus high-dose dexamethasone (n = 153) in patients with relapsed MM who were refractory to both lenalidomide and bortezomib.²²⁵ After a median follow-up of 10 months, PFS, the primary endpoint of the study, was significantly longer in patients who received pomalidomide and low-dose dexamethasone compared with those who received high-dose dexamethasone (4.0 vs. 1.9 months; HR, 0.45; $P < .0001$).²²⁶ The median OS was significantly longer in the patients who received pomalidomide and low-dose dexamethasone as well (12.7 months vs. 8.1 months; HR = 0.74; $P = .0285$).²²⁶ The most common hematologic grade 3 and 4 adverse effects found to be higher with the low-dose dexamethasone compared with the high-dose dexamethasone were neutropenia and pneumonia.²²⁶ Other phase III studies of pomalidomide plus low-dose dexamethasone in combination with other agents (eg, bortezomib) are currently ongoing (Clinical Trial ID: NCT01734928). A European multicenter, single-arm, open-label phase IIb trial evaluated the safety and efficacy of pomalidomide and low-dose dexamethasone in a large patient population (N = 604).²²⁷ The median PFS reported was 4.2 months and OS was 11.9 months. Whether the patients received prior lenalidomide or bortezomib, the PFS, OS, and ORR reported were similar.²²⁷ The results of this trial are consistent with those observed in the pivotal MM-003 trial.²²⁶

In addition, several complementary phase II studies have been published evaluating the use of pomalidomide and dexamethasone in

patients with MM relapsed/refractory to lenalidomide and/or bortezomib. A phase II study investigated two different dose regimens of pomalidomide and dexamethasone in 84 patients with advanced MM. Pomalidomide (4 mg) was given orally on days 1 to 21 or continuously over a 28-day cycle, and dexamethasone (40 mg) was given orally once weekly.²²⁸ ORR was 35% and 34% for patients in the 21-day and 28-day groups, respectively. With median follow-up of 23 months, median duration of response, PFS, and OS were 7.3, 4.6, and 14.9 months across both groups, respectively. All patients experienced similar adverse events in both groups. The adverse events were primarily due to myelosuppression.²²⁸ Another phase II trial evaluated two doses of pomalidomide 2 or 4 mg/d with dexamethasone 40 mg weekly in heavily pre-treated patients (n = 35).²²⁹ The ORR in the 2-mg cohort was 49% versus 43% in the 4-mg cohort. OS at 6 months was 78% and 67% in the 2- and 4-mg cohort, respectively. Myelosuppression was the most common toxicity.²²⁹

The FDA has approved pomalidomide for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. The FDA-recommended dose and schedule of pomalidomide is 4 mg orally on days 1 to 21 of repeated 28-day cycles with cycles repeated until disease progression along with the recommendation to monitor patients for hematologic toxicities, especially neutropenia.

Based on the above data, the NCCN panel has included pomalidomide plus dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1). For steroid-intolerant



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individuals, the NCCN Multiple Myeloma Panel suggests considering pomalidomide monotherapy.

Pomalidomide/Bortezomib/Dexamethasone

Pomalidomide/bortezomib/dexamethasone has been evaluated in patients with relapsed/refractory MM in early phase I/II studies.²³⁰⁻²³² Based on the encouraging ORRs observed in these studies, the triplet is currently being evaluated in an ongoing phase III study.²³³

The NCCN panel has now included pomalidomide/bortezomib/dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide/Carfilzomib/Dexamethasone

Based on the encouraging results of the phase I study²³⁴ a phase II study was carried out to evaluate the safety and efficacy of pomalidomide, carfilzomib, and dexamethasone in lenalidomide refractory and proteasome-naïve/sensitive patients with relapsed/refractory MM. After a median of 7.2 cycles (range = 0.6–27.1 cycles), PR reported was 84%, MR was 91%, VGPR was 26%, and CR/near CR was 12%.²³⁵ After a median follow-up of 18 months (range = 1–39 months), the median PFS for all 55 patients was 12.9 months and the estimated 18-month OS was 86.5%.²³⁵

The NCCN panel has now included this regimen pomalidomide/carfilzomib/dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide/Cyclophosphamide/Dexamethasone

A phase II study compared the combination of pomalidomide/cyclophosphamide/dexamethasone to pomalidomide/dexamethasone in patients (n = 70) with relapsed/refractory MM who had received more than 2 prior therapies.²³⁶

The triple-drug combination significantly improved the ORR (≥PR, 64.7% vs. 38.9%; $P = .0355$). The median PFS reported was 9.5 months versus 4.4 months. There were no significant differences in AE reports between the treatment arms; grade 3 and 4 anemia, neutropenia, and thrombocytopenia, respectively, were reported in 11%, 31%, and 6% of patients treated with pomalidomide/dexamethasone and 24%, 52%, and 15% of patients treated with the triplet regimen.²³⁶ Similar results were reported by a single center retrospective study²³⁷ of patients (n = 20) with relapsed/refractory MM who received pomalidomide/cyclophosphamide/dexamethasone until transplant or disease progression was reported.²³⁶ Response to the triple-drug regimen was 63%, with nearly half of patients (42%) responding after 1 cycle with a median time to response of 3 cycles. One-year median PFS was 80.7% and 65% of patients were relapse-free.²³⁷

Based on the above phase II trial data, the NCCN panel has included pomalidomide/cyclophosphamide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Daratumumab

Daratumumab is a human IgG kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells.²⁰⁰ In a phase I/II study, patients who had received more than 3 lines of therapy including an IMiD and a PI or were double refractory to PI and IMiD were

randomized to 2 different doses of daratumumab (8 mg/kg vs. 16 mg/kg). ORR was 29.2% (3 sCR, 10 VGPR, and 18 PR). Median duration of response was 7.4 months and median time to progression was 3.7 months. The estimated 1-year OS rate was 65%.²⁰¹ Adverse events reported were fatigue (39.6%), anemia (33.0%), nausea (29.2%), and thrombocytopenia (25.5%). Grade 1 and 2 infusion-related reactions were seen in 42.5% of patients, mainly during first infusion. No patients discontinued the study due to infusion-related reactions.²⁰¹

Based on the above phase II results and FDA approval, the panel has added daratumumab as an option for the treatment of patients with MM who have received at least 3 prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and IMiD.

Daratumumab/Pomalidomide/Dexamethasone

The combination of daratumumab/pomalidomide/dexamethasone was evaluated in an open-label, multicenter, phase 1b study (MMY1001). This study included patients (n = 103 patients) who had received at least two prior lines of therapy (excluding daratumumab or pomalidomide).²³⁸ At a median follow-up of 13.1 months, The ORR was 60%. The median PFS and median OS were 8.8 and 17.5 months, respectively, and estimated survival at 1 year was 66%.²³⁸ Toxicities reported were similar to those seen in other trials of pomalidomide and daratumumab, except for increase in neutropenia.²³⁸

Based on the above data, the NCCN panel has included daratumumab/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least 2 prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Ixazomib/Dexamethasone

Data from two phase I studies of single-agent ixazomib in patients with relapsed/refractory MM established the maximum tolerated dose of ixazomib to be 2.0 mg/m² on a twice-weekly schedule and 2.97 mg/m² on a weekly schedule.^{239,240} The patients in these studies had multiple prior lines of therapy (median of 4 prior lines of therapy in both studies). In the study with the weekly schedule,²³⁹ out of 30 evaluable patients the rate of PR or better (≥PR) was 27%. In the twice-weekly schedule, out of 55 evaluable patients ≥PR rate was 15%.²⁴⁰ Adverse events, grade ≥3, were reported in 78% (drug-related in 62%) of patients on the twice-weekly schedule²⁴⁰ and 65% (53%) of patients on the weekly schedule.²³⁹ These included thrombocytopenia (37%), neutropenia (17%), and skin and subcutaneous tissue disorders (8%) on the twice-weekly schedule, and thrombocytopenia (33%), neutropenia (18%), and diarrhea (17%) on the weekly schedule. Peripheral neuropathy was reported in 17% (drug-related in 12%) of patients, with no grade 3 events, on the twice-weekly schedule.²⁴⁰ On the weekly schedule drug-related peripheral neuropathy was reported in 20% of patients (2% grade 3).²³⁹

Subsequently, phase II trials were designed to evaluate ixazomib with or without dexamethasone in patients with myeloma who have limited prior exposure to bortezomib.^{241,242} In one trial, patients (n = 33) with relapsed MM received weekly ixazomib 5.5 mg and had dexamethasone added for suboptimal response or disease progression (in 67% of patients). Six additional patients achieved a PR after the addition of dexamethasone.²⁴¹ The ORR (≥PR) with or without the addition of dexamethasone reported was 34%.²⁴¹ Adverse events, grade ≥3, were reported in 78%. The most common adverse events observed included thrombocytopenia, fatigue, nausea, and diarrhea.²⁴¹

Another phase II study evaluated two doses of weekly ixazomib (arm A, 4 mg and arm B, 5.5 mg) plus weekly dexamethasone (40 mg) in patients (n = 70) with relapsed MM. The patients enrolled in the trial had not been previously treated with a proteasome inhibitor (including bortezomib) or had received less than 6 cycles of therapy with bortezomib and had a PR or better and no progression at the time of discontinuation.²⁴² The ORRs were 31% in arm A (95% CI, 17–49) and 51% (95% CI, 34–69) in arm B. Among the patients with no prior bortezomib exposure the response rates were 38% for arm A and 52% for arm B.²⁴² The most common toxicities reported in this trial were fatigue, thrombocytopenia, diarrhea, and nausea with more grade 3 toxicities among arm B. Peripheral neuropathy, possibly related to ixazomib, was seen in 55% (only grade 1 or 2) in arm A and 43% (2 patients with grade 3) in arm B.²⁴²

Based on the above phase I/II trial data, the NCCN panel has included ixazomib/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Ixazomib/Pomalidomide/Dexamethasone

In phase I Alliance A061202 study (n= 22), 32% of patients were refractory to a lenalidomide/PI combination and 68% were refractory to the sequential use of these drugs. The majority of patients (65%) had high-risk cytogenetics. More than half the patients experienced grade 3 and 4 neutropenia, lymphopenia, and reductions in white blood cell count. Peripheral neuropathy, rash, diarrhea, and other side effects were limited to grades 1 and 2. The ORR was 55% in those with PI- or lenalidomide-refractory disease and responses were found to be durable over time.²⁴³

Another phase I/II study studied the safety and efficacy of ixazomib/pomalidomide/dexamethasone in patients who had multiple

prior therapies, were refractory to lenalidomide alone, or were refractory to lenalidomide and bortezomib, or lenalidomide, bortezomib and carfilzomib.²⁴⁴ The ORR was 33% and 40% with 2 different doses of ixazomib.²⁴⁴

Considering promising preliminary response rates, especially in patients refractory to both lenalidomide and a PI, the NCCN panel has included ixazomib/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least 2 prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Elotuzumab/Bortezomib/Dexamethasone

Numerous randomized trials have shown that 3-drug combinations have been shown to be consistently more effective than 2-drug combinations for the treatment of MM. A phase II trial studied the effect of addition of elotuzumab to bortezomib/dexamethasone in patients with relapsed/refractory MM.²⁴⁵

Interim analysis results demonstrated a 28% reduction in risk of disease progression or death for patients in the elotuzumab-containing triple-drug arm compared to patients treated with bortezomib/dexamethasone (HR, 0.72; 70% CI, 0.59–0.88). Median PFS was significantly higher in the elotuzumab-containing arm (9.7 months vs. 6.9 months). After 2 years the addition of elotuzumab continued to show an efficacy benefit compared to bortezomib/dexamethasone alone with a 24% relative risk reduction in PFS (HR, 0.76; 70% CI, 0.63–0.91).²⁴⁵

Based on the above phase II trial data, the NCCN panel has included elotuzumab/bortezomib/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Panobinostat/Carfilzomib

A multicenter, phase I/II study assessed the safety and efficacy of the combination of panobinostat and carfilzomib in patients with relapsed/refractory MM who had relapsed after at least one prior treatment.²⁴⁶ The phase I of the study was to determine the maximum tolerable dose of panobinostat and carfilzomib. The primary endpoint of the phase II was ORR.

No dose-limiting toxicities were observed at any of the planned dose levels in the phase I study. Of the 42 evaluable patients in phase II, the ORR was 67% and the clinical benefit rate was 79%.²⁴⁶ The ORR was 67% for patients refractory to prior PI treatment and 75% for patients refractory to prior immune-modulating drug treatment. At a median follow-up of 17 months, median PFS was 7.7 months.²⁴⁶ Grade 3/4 treatment-related adverse events included thrombocytopenia (38%), neutropenia (21%), fatigue (11%), anemia (9%), hypertension (9%), and diarrhea (7%).²⁴⁶

The maximum tolerated dose of carfilzomib and panobinostat was not reached with the 4 dosing schedules in the first phase I study;²⁴⁶ two additional dosing schedules were evaluated. The maximum planned dose from the first study was 30 mg panobinostat plus 20/45 mg/m² of carfilzomib. In this study,²⁴⁶ the dose of carfilzomib was escalated to 20/56 mg/m² in one cohort. Due to dose reductions of panobinostat in the first study, the second cohort in this study explored 20 mg of panobinostat and carfilzomib 20/56 mg/m². The most common adverse events grade ≥3 were thrombocytopenia (31%), fatigue (4%), and diarrhea (4%). The ORR was 82% (34% ≥VGPR and 48% PR). The clinical benefit rate was 91%.

Based on promising phase I/II data, the NCCN panel has added panobinostat in combination with carfilzomib as a treatment option for patients with previously treated MM.

Panobinostat/Bortezomib/Dexamethasone

Panobinostat is a pan-deacetylase inhibitor that epigenetically modulates class I and II HDAC enzymes.²⁴⁷ Recently, the FDA approved the use of panobinostat in combination with bortezomib and dexamethasone for patients with relapsed/refractory MM who have had at least two prior therapies with regimens containing an IMiD and bortezomib.

The approval was based on the results of a randomized placebo-controlled phase III study, PANORAMA-1. The study randomized 768 patients with MM who had received prior treatment with an IMiD and bortezomib to receive bortezomib and dexamethasone along with either panobinostat or placebo. The results showed an improved median PFS with the panobinostat-containing regimen compared with the control arm (11.99 months [95% CI; 10.33–12.94 months] vs. 8.08 months [95% CI; 7.56–9.23 months]; HR, 0.63; 95% CI, 0.52–0.76; *P* < .0001) along an increased depth of response.²⁴⁸ The final OS data from this study are not yet available.

The regimen containing panobinostat is associated with significant toxicity. Serious adverse events were reported in 228 (60%) of 381 patients in the panobinostat group and 157 (42%) of 377 patients in the placebo group. Common grade 3–4 laboratory abnormalities and adverse events were more in the panobinostat group versus the control group including thrombocytopenia 67% vs. 31%), lymphopenia (53% vs. 40%), diarrhea (26% vs. 8%), fatigue (4% vs. 2%), and peripheral neuropathy (18% vs. 5%).²⁴⁸



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The PANORAMA-2 is a phase II single-arm, multicenter trial that evaluated the combination of panobinostat with bortezomib and dexamethasone in patients who had relapsed disease, refractory to bortezomib (N = 55).²⁴⁹ Patients in this study achieved an ORR of 34.5% with the panobinostat-containing regimen.²⁴⁹ The median PFS was 5.4 months and OS had not been reached at a median follow-up of 8.3 months.²⁴⁹ Common grade 3/4 adverse events included thrombocytopenia (63.6%), diarrhea (20.0%), and fatigue (20.0%).²⁴⁹

The NCCN Multiple Myeloma Panel has included panobinostat in combination with bortezomib and dexamethasone as a category 1 option for patients who have received at least two prior therapies, including an immunomodulator and bortezomib.

Panobinostat/Lenalidomide/Dexamethasone

A single-center, phase II study evaluated the safety and efficacy of the oral regimen containing panobinostat with lenalidomide and dexamethasone in patients (n = 27) with relapsed or relapsed/refractory MM (including those refractory to IMiD and PIs).²⁵⁰ ORR was 41% and median PFS was 7.1 months. In lenalidomide-refractory patients (n = 22), the ORR was 36% and median PFS was 6.5 months.²⁵⁰ The expected hematologic toxicities seen reported and GI toxicities seen with the combination of HDAC inhibitors and bortezomib was not seen in this trial.²⁵⁰

Based on the encouraging ORR and PFS in iMiD-refractory patients, the NCCN Multiple Myeloma Panel has included panobinostat with lenalidomide and dexamethasone for patients who have received at least two prior therapies, including an immunomodulator and bortezomib.

Regimens Useful Under Certain Circumstances for Previously Treated MM

In a trial by Knop and colleagues, 31 patients who had experienced relapse after autologous transplantation were enrolled to receive increasing doses of bendamustine.²⁵¹ The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90–100 mg/m²). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has reported that bendamustine is effective and tolerable in patients with advanced progressive MM, with an ORR of 36%.²⁵²

The Eastern Cooperative Oncology Group (ECOG) studied treatment with high-dose cyclophosphamide in poor-risk myeloma patients who had disease refractory to prior chemotherapy.²⁵³ The overall objective response rate reported was 43% (29% response rate in patients refractory to prior therapy with cyclophosphamide).²⁵³

Patients with an aggressive relapse may need multi-drug combinations such as DCEP,²⁵⁴⁻²⁵⁶ TD-PACE (thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide),^{257,258} and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide)²⁵⁹⁻²⁶¹ for effective disease control.

Bendamustine is currently a treatment option for relapsed/refractory MM. High-dose cyclophosphamide is included as an option in the NCCN Guidelines for patients with relapsed/refractory MM.

The NCCN Guidelines include bendamustine, high-dose cyclophosphamide, DCEP, DT-PACE, and VTD-PACE as therapeutic options that are useful under certain circumstances for patients with previously treated MM.



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Supportive Care Treatment for Multiple Myeloma

Important advances have been made in adjunctive treatment/supportive care of patients with MM. This involves careful patient education about the probable side effects of each drug, the drug combinations being used, and the supportive care measures required. Supportive care can be categorized into those measures required for all patients and those that address specific drugs.

Bony manifestations of myeloma, in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of IV pamidronate (a bisphosphonate) can decrease pain and bone-related complications, improve performance status, and, importantly, preserve quality of life in patients with Durie-Salmon stage III MM and at least one lytic lesion.^{262,263} Zoledronic acid has equivalent benefits.²⁶⁴ Results from the study conducted by Zervas et al²⁶⁵ show a 9.5-fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should have a dental exam prior to start of bisphosphonate therapy and should be monitored for osteonecrosis of the jaw.

The MRC Myeloma IX study examined effects of zoledronic acid versus clodronate (a bisphosphonate not currently FDA approved) in patients with MM initiating chemotherapy regardless of bone disease. The patients were randomized to receive zoledronic acid (n = 981) or clodronic acid (n = 979). Zoledronic acid was reported to reduce mortality and significantly improve PFS.²⁶⁶ Patients on clodronate and zoledronic acid had similar occurrence of acute renal failure and

treatment-related serious adverse events. Zoledronic acid was associated with higher rates of confirmed osteonecrosis of the jaw than was clodronic acid.²⁶⁶⁻²⁶⁸ The study reanalyzed and recently reported survival outcomes. After an extended follow-up (median, 5.9 years), in addition to PFS, the OS was also significantly improved (52 vs. 46 months; HR, 0.86; $P = .01$) compared with clodronic acid.²⁶⁹ The long-term rates of osteonecrosis of the jaw were also observed to be higher with zoledronic acid compared with clodronate (3.7% vs. 0.5%; $P = .0001$).²⁶⁹

A recent meta-analysis of 20 randomized controlled trials of comparing bisphosphonates with either placebo or a different bisphosphonate as a comparator concluded that adding bisphosphonates to the treatment of MM reduces vertebral fractures and probably reduces pain. Whether zoledronate is superior to pamidronate and other bisphosphonates remains to be determined.²⁷⁰

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates for all patients receiving myeloma therapy for symptomatic disease regardless of documented bone disease (category 1). In patients with smoldering or stage I MM, according to the NCCN panel, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

Low-dose radiation therapy (10–30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.⁴⁸ Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose



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therapy and hematopoietic SCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from myeloma bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration, bisphosphonates, denosumab,²⁷¹ steroids, and/or calcitonin. Among the bisphosphonates (zoledronic acid, pamidronate, and ibandronate), the NCCN Multiple Myeloma Panel members prefer zoledronic acid for treatment of hypercalcemia.^{264,272,273}

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.²⁷⁴ Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Erythropoietin therapy may be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning^{275,276} (see [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)). Daratumumab can interfere with cross-matching and red blood cell antibody screening. The NCCN panel recommends performing type and screen prior to receiving daratumumab to inform future matching.

To prevent infection: 1) IV immunoglobulin therapy should be considered for recurrent, life-threatening infections; 2) pneumococcal and influenza vaccine should also be considered; and 3) *Pneumocystis*

carinii pneumonia (PCP), herpes, and antifungal prophylaxis is recommended if a high-dose regimen is used. PIs (bortezomib, carfilzomib, and ixazomib) and daratumumab treatment has been associated with an incidence of herpes zoster.^{73,74} Herpes prophylaxis is recommended in patients receiving PI or daratumumab therapy.⁷² (See [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)).

Thrombosis is relatively common when thalidomide or lenalidomide is used with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see [NCCN Guidelines for Venous Thromboembolic Disease](#)) is recommended when IMiDs are used in combination therapy during induction.^{106,277,278}

Hydration should be maintained and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided to decrease the chances of renal dysfunction. According to the NCCN Multiple Myeloma Panel members, the use of plasmapheresis to improve renal function is a category 2B recommendation. The use of IV contrast media should also be avoided in patients with renal impairment. Renal function should be monitored with chronic use of bisphosphonates.



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